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DNA-TARGETED BENZOTRIAZINE 1,4-DIOXIDES AND THEIR USE IN CANCER THERAPY

REFERENCE TO GOVERNMENT CONTRACT

The invention described herein was made in the course of work under grant or contract from the United States Department of Health and Human Services. The United States Government has certain rights to this invention.

TECHNICAL FIELD

The present invention relates to DNA-targeted 1,2,4-benzotriazine-1,4-dioxides and related analogues, to their preparation, and to their use as hypoxia-selective drugs and radiosensitizers for cancer therapy, both alone or in combination with radiation and/or other anticancer drugs.

BACKGROUND TO THE INVENTION

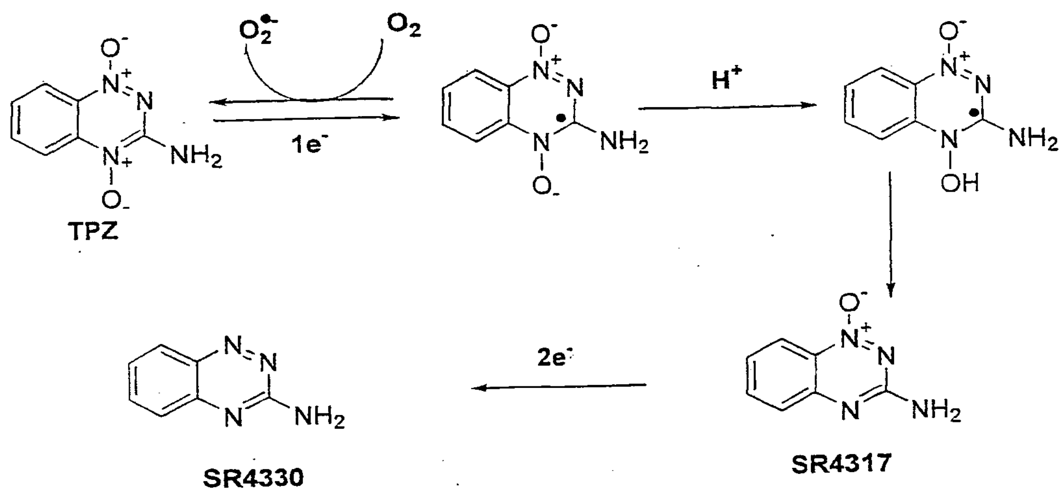
It has been established that many human tumors contain a significant hypoxic fraction of cells (Kennedy et al., *Int. J. Radiat. Oncol. Biol. Phys.*, **1997**, 37, 897-905; Movsas et al., *Urology,* **1999**, 53, 11-18). The presence of hypoxic cells arises because of chaotic growth and an inefficient microvasculature system within the tumor, which leads to large intercapillary distances and variable blood flow. Reduction of oxygen tension in tumors leads to radioresistence. This reduction of oxygen tension causes up to a three-fold increase in radiation dose being required to kill anoxic tumor cells. A link has been identified between the presence of tumor hypoxia and failure of local control by radiation therapy (Brizel et al., *Radiother. & Oncol.*, **1999**, 53, 113-117). This phenomenon of tumor hypoxia has been exploited in the development of a class of anticancer agents termed 'bioreductive drugs' (Brown et al., Semin. Radiat. Oncol., 1966, 6, 22-36; Denny et al., *Br. J. Cancer*, **1996**, 74 (Suppl. XXVII) 32-38; Stratford & Workman, *Anti-Cancer Drug Des.*, **1998**, 13, 519-528). These agents are selectively active against hypoxic cells in tumors by targeting the DNA of these cells. The agents cause irreversible damage to the DNA of the tumor cells, thereby causing the destruction and breakdown of the tumor.

Tirapazamine (TPZ, 3-amino-1,2,4-benzotriazine 1,4-dioxide) is a bioreductive agent (Kelson et al., *Anti-Cancer Drug Des.*, **1998**, 13, 575-592; Lee et al., WO 9104028,

April 1991) and is undergoing clinical trials in combination with radiotherapy and various chemotherapeutics, notably cisplatin (Denny & Wilson, *Exp. Opin. Invest. Drugs*, **2000**, 9, 2889-2901).

TPZ is activated by one electron reductases (Patterson et al., *Anti-Cancer Drug Des.* **1998** 13, 541-573; Denny & Wilson, *Exp. Opin. Invest. Drugs*, **2000**, 9, 2889-2901) to form a radical anion (Scheme A). This TPZ radical anion may be oxidized back to TPZ by molecular oxygen under aerobic conditions.

Scheme A.



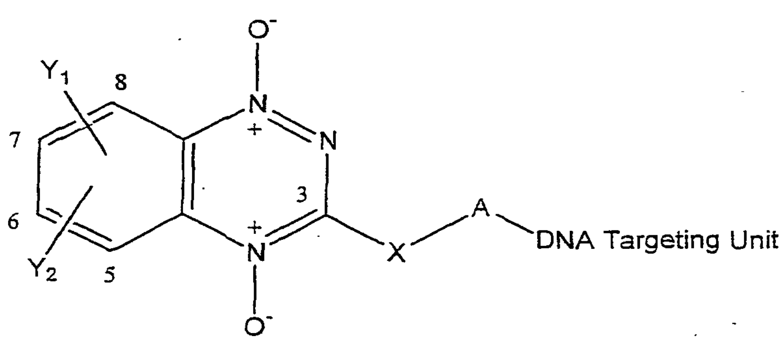
Under hypoxic conditions the radical or species ultimately derived from TPZ can interact with DNA, although the exact mechanism is unclear (Jones et al., *Cancer Res.*, **1996**, 56, 1584-1590; Daniels et al., *Chem. Res. Toxicol.*, **1998**, 11, 1254-1257; Hwang et al., *Biochem.*, **1999**, 38, 14248-14255). TPZ causes DNA double-strand breaks under anoxic conditions (Jones et al., *Cancer Res.*, **1996**, 56, 1584-1590) and these results correlate with cytotoxicity (Dorie et al., *Neoplasia*, **1999**, 1, 461-467). Reversible one-electron reduction of TPZ that gives rise to a reactive radical species that is thought to be the basis for selective toxicity to hypoxic cells. Two electron reduction of TPZ or further reduction of the TPZ radical produces the metabolite 1-oxide (SR 4317) and further reduction gives the nor-oxide (SR 4330) (Baker et al., *Cancer Res.*, **1988**, 48, 5947-5952; Laderoute & Rauth, *Biochem Pharmacol.*, **1986**, 35, 3417-3420) (Scheme A). The metabolites (SR 4317) and (SR 4330) are both inactive under aerobic or hypoxic conditions.

It is also known that reactive species can be effectively targeted to DNA by attachment to DNA-affinic carriers. Thus, the intrinsic cytotoxicities and *in vivo* potencies of aniline mustards can be significantly increased (up to 100-fold), and the usual dependence of cytotoxicity on mustard reactivity lowered, by targeting to DNA via a 9-aminoacridine carrier (Gourdie et al., *J. Med. Chem.*, **1990**, 33, 1177-1185). DNA alkylation patterns can also be significantly altered (Prakash et al., *Biochem.*, **1990**, 29, 9799-9807; Boritzki et al., *Chem. Res. Toxicol.*, **1994**, 7, 41-46). Alkylation of DNA by DNA-targeted compounds is more rapid than with the corresponding untargeted compounds (O'Connor et al., *Chem.-Biol. Int.*, **1992**, 85, 1-14). However, the extent of DNA binding needs to be carefully adjusted to achieve effective targeting without significantly compromising the transport/diffusion properties (Hicks et al., *J. Pharmacol. Exp. Therapeut.* **2001**, 297,1088-1098; Hicks et. al, *Brit. J. Cancer*. **1997**, 76, 894-903). Binding ability can be varied by alteration of both the chromophore and substituents on the DNA targeted compound (Palmer et al., *J. Med. Chem.*, **1988**, 31, 707-712).

It is an object of the present invention to utilize DNA-affinic carriers in combination with benzotriazine 1,4-dioxides to target DNA for cancer therapy purposes, or to at least provide the public with a useful choice.

DISCLOSURE OF THE INVENTION

In a first aspect, the present invention provides a compound of Formula **I**,



I

wherein

Y_1 and Y_2 at one or more of the available carbons 5-8 on the benzo ring: are each independently selected from the following groups: halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl and morpholino;

wherein each R is independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the said optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

R can also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2, $NR^2{}_2$ or $N(OH)R^2$ wherein each R^2 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

wherein X represents NH, NMe, CH_2, SO, SO_2, or O;

A represents an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^3, $NR^3{}_2$, or $N(OH)R^3$ wherein each R^3 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain is optionally interrupted or extended by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, where each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, $NR^5{}_2$ or $N(OH)R^5$ wherein each R^5 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and

wherein the DNA-targeting unit is any moiety of a molecular weight below 700 Daltons that has an association constant (K) for binding to double-stranded random-sequence DNA of $>10^3$ M^{-1} at an ionic strength of 0.01 M at 20 °C,

or a pharmacologically acceptable salt thereof.

The definition of the DNA targeting unit above refers to double-stranded random-sequence DNA. An example of such double-stranded random-sequence DNA is DNA extracted from calf thymus.

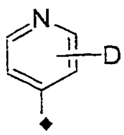
A preferred compound of Formula I is one in which X is NH or CH_2.

A further preferred compound of Formula I is one in which Y_1 and Y_2 each represent H.

A further preferred compound of Formula I is one in which Y_1 represents OMe

A preferred embodiment of Formula I are compounds wherein A is selected from $-(CH_2)_6NH-$, $-(CH_2)_3NH(CH_2)_3NHCO-$, $-(CH_2)_3NMe(CH_2)_3NHCO-$, $-(CH_2)_3NH-$, $-(CH_2)_2NH(CH_2)_2NHCO-$ or $-(CH_2)_2NMe(CH_2)_2NHCO-$.

A further preferred embodiment of Formula I are compounds wherein the DNA-targeting unit is selected from one of formulae **II- XVI**,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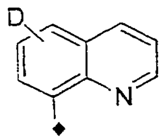
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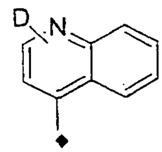
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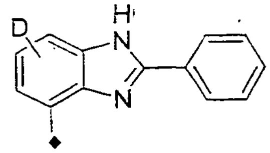
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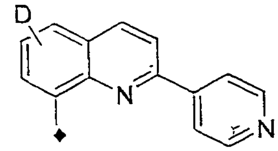
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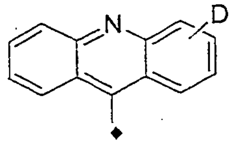
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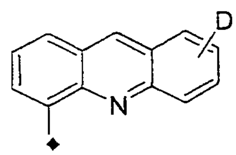
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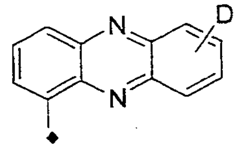
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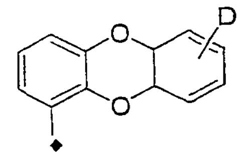
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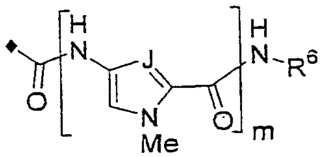
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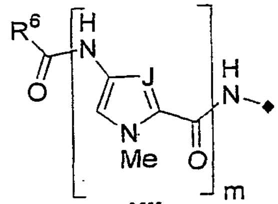
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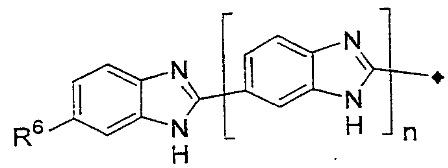
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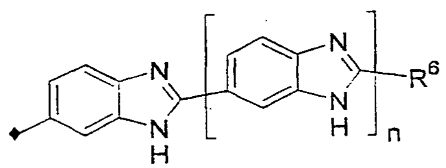
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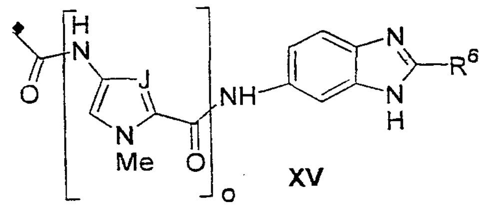
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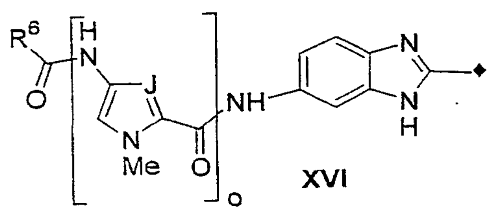

XVI

wherein in structures **XI-XVI** R^6 is independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^7 NO_2, NH_2, NHR^7, NR^7R^7, SR^7, imidazolyl, R^7-piperazinyl, morpholino, SO_2R^7, CF_3, CN, CO_2H, CO_2R^7, CHO, COR^7, $CONH_2$, $CONHR^7$, $CONR^7R^7$;

R^6 can also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^7, NH_2, NHR^7, NR^7R^7, SH, SR^7, imidazolyl, R^7-piperazinyl, morpholino, SO_2R^7, CF_3, CN, CO_2H, CO_2R^7, CHO, COR^7, $CONH_2$, $CONHR^7$, $CONR^7R^7$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^7 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR^8, NH_2, NHR^8, NR^8_2 or $N(OH)R^8$ wherein each R^8 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH;

D represents up to four of the following groups as substituents at any available ring carbon position; H, R^9, hydroxy, alkoxy, halogen, NO_2, NH_2, NHR^9, NR^9_2, SH, SR^9, SO_2R^9, CF_3, CN, CO_2H, CO_2R^9, CHO, COR^9, $CONH_2$, $CONHR^9$ or $CONR^9R^9$, cyclic alkylamino, imidazolyl, alkylpiperazinyl and morpholino, wherein each R^9 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR^{10}, NH_2, NHR^{10}, NR^{10}_2 or $N(OH)R^{10}$ wherein each R^{10} is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH;

and wherein any available ring carbon position of formulae **II** - **XVI** can also be optionally replaced by –N- when the valency and configuration of the formula allows, the point of attachment of formulae **II**- **XVI** to the A group defined above is represented by ◆; and wherein in formulae **XI, XII,** , m is selected from 2, 3 or 4, and wherein in formulae **XI, XII, XV** and **XVI**, J is selected from CH or N; and wherein in formulae **XIII** and **XIV** n is selected from 0, 1 or 2; and wherein in formulae **XV** and **XVI** o is selected from 1 and 2.

A preferred embodiment of formula I is one in which the DNA targeting unit is selected from one of formulae IV, V, VI, VII, VIII, or IX.

A preferred embodiment of formula I is one in which D of the DNA targeting unit of Formulae II - X is H or Me.

Further preferred compounds of formula I include the following

wherein X is NH-, Y_1 is H, Y_2 is H, A is $-(CH_2)_6NH-$, the DNA targeting unit represents formula VII and D is H;

wherein X is NH-, Y_1 is H, Y_2 is H, A is $-(CH_2)_3NH(CH_2)_3NHCO$-, the DNA targeting unit represents formula VIII and D is H;

wherein X is NH-, Y_1 is H, Y_2 is H, A is $-(CH_2)_2NH(CH_2)_2NHCO$-, the DNA targeting unit represents formula VIII and D is H;

wherein X is NH-, Y_1 is H, Y_2 is H, A is $-(CH_2)_3NMe(CH_2)_3NHCO$-, the DNA targeting unit represents formula VIII and D is H;

wherein X is NH-, Y_1 is H, Y_2 is H, A is $-(CH_2)_3NMe(CH_2)_3NHCO$-, the DNA targeting unit represents formula IV and D is H;

wherein X is NH-, Y_1 is H, Y_2 is H, A is $-(CH_2)_3NMe(CH_2)_3NHCO$-, the DNA targeting unit represents formula VI and D is H;

wherein X is NH-, Y_1 is H, Y_2 is H, A is $-(CH_2)_3NMe(CH_2)_3NHCO$-, the DNA targeting unit represents formula VIII and D is Me;

wherein X is NH-, Y_1 is H, Y_2 is H, A is $-(CH_2)_3NMe(CH_2)_3NHCO$-, the DNA targeting unit represents formula IX and D is Me;

wherein X is NH-, Y_1 is 7-$MeOCH_2CH_2O$-, Y_2 is H, A is $-(CH_2)_3NMe(CH_2)_3NHCO$-, the DNA targeting unit represents formula VIII and D is H;

wherein X is CH_2-, Y_1 is H, Y_2 is H, A is $-(CH_2)_2NMe(CH_2)_3NHCO$-, the DNA targeting unit represents formula VIII and D is H;

wherein X is NH-, Y_1 is H, Y_2 is H, A is $-(CH_2)_2NMe(CH_2)_3NHCO$-, the DNA targeting unit represents formula XI and D is H;

wherein X is NH-, Y_1 is 7-Me, Y_2 is H, A is $-(CH_2)_3NMeH(CH_2)_3NHCO$-, the DNA targeting unit represents formula VIII and D is H;

wherein X is NH-, Y_1 is 7-Me, Y_2 is H, A is $-(CH_2)_3NMe(CH_2)_3NHCO$-, the DNA

targeting unit represents formula VI and D is H;

wherein X is NH-, Y_1 is 6-Me, Y_2 is H, A is $-(CH_2)_3NMe(CH_2)_3NHCO-$, the DNA targeting unit represents formula VIII and D is H;

wherein X is NH-, Y_1 is 6-Me, Y_2 is H, A is $-(CH_2)_3NMe(CH_2)_3NHCO-$, the DNA targeting unit represents formula VI and D is H;

wherein X is NH-, Y_1 is H, Y_2 is H, A is $-(CH_2)_2NMe(CH_2)_2NHCO-$, the DNA targeting unit represents formula VIII and D is H;

wherein X is NH-, Y_1 is H, Y_2 is H, A is $-(CH_2)_2NMe(CH_2)_2NHCO-$, the DNA targeting unit represents formula VI and D is H;

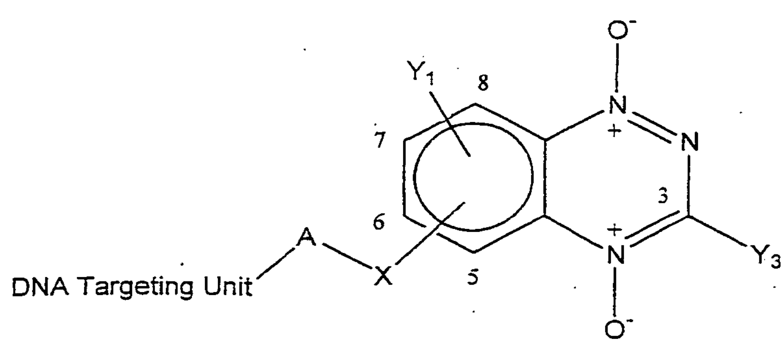
wherein X is NH-, Y_1 is H, Y_2 is H, A is $-(CH_2)_2NMe(CH_2)_2NHCO-$, the DNA targeting unit represents formula XI and D is Me;

wherein X is NH-, Y_1 is H, Y_2 is H, A is $-(CH_2)_2NMe(CH_2)_2NHCO-$, the DNA targeting unit represents formula VIII and D is Me;

wherein X is NH-, Y_1 is H, Y_2 is H, A is $-(CH_2)_2NH(CH_2)_2NHCO-$, the DNA targeting unit represents formula VI and D is H; and

wherein X is NH-, Y_1 is H, Y_2 is H, A is $-(CH_2)_2NH(CH_2)_2NHCO-$, the DNA targeting unit represents formula VIII and D is Me.

In a second aspect, the present invention provides a compound of Formula **I′**,



I′

wherein

Y_1 represents at one or more of the available carbons 5-8 on the benzo ring the following groups:

halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl and morpholino;

Y_3 is selected from the following groups halo, H, R, OR, NH_2, NHR, NR_2, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl and morpholino;

wherein each R of groups Y_1 and Y_3 is independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

R can also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2, $NR^2{}_2$ or $N(OH)R^2$ wherein each R^2 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

wherein X represents NH, NMe, CH_2, SO, SO_2, or O;

A represents an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^3, $NR^3{}_2$ or $N(OH)R^3$ wherein each R^3 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN,

CO_2H or SH; and wherein the optionally substituted C_{2-12} alkyl chain is optionally interrupted by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, where each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, NR^5_2 or $N(OH)R^5$ wherein each R^5 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and

wherein the DNA-targeting unit is any moiety of a molecular weight below 700 Daltons that has an association constant (K) for binding to double-stranded random-sequence DNA of $>10^3$ M^{-1} at an ionic strength of 0.01 M at 20 °C,

or a pharmacologically acceptable salt thereof.

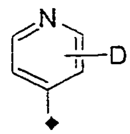
The definition of the DNA targeting unit above refers to double-stranded random-sequence DNA. An example of such double-stranded random-sequence DNA is DNA extracted from calf thymus.

A preferred compound of Formula I′ is one in which X is O, NH or CH_2.

A further preferred compound of Formula I′ is one in which Y_1 represents H.

A preferred embodiment of Formula I′ are compounds wherein A is selected from $-(CH_2)_6NH-$, $-(CH_2)_3NH(CH_2)_3NHCO-$, $-(CH_2)_3NMe(CH_2)_3NHCO-$, $-(CH_2)_3NH-$, $-(CH_2)_2NH(CH_2)_2NHCO-$ or $-(CH_2)_2NMe(CH_2)_2NHCO-$.

A further preferred embodiment of Formula I′ are compounds wherein the DNA-targeting unit is selected from one of formulae **II- XVI**,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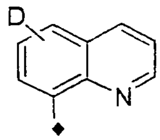
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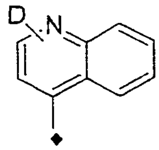
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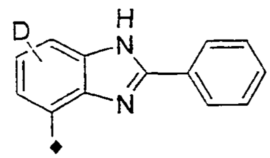
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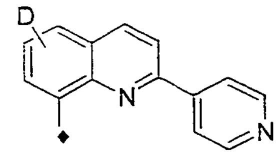
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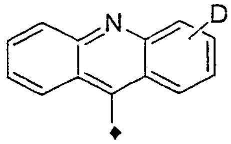
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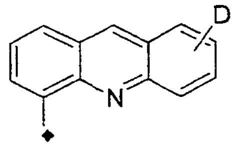
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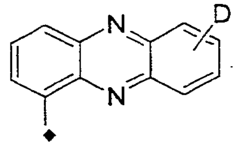
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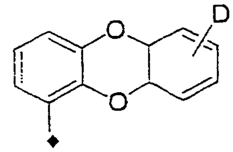
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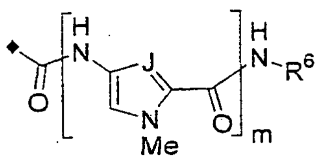
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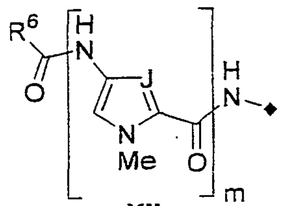
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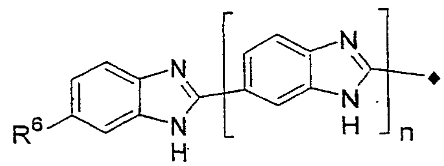
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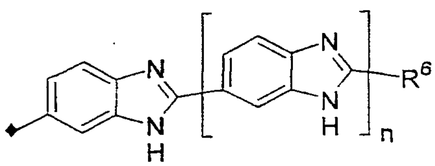
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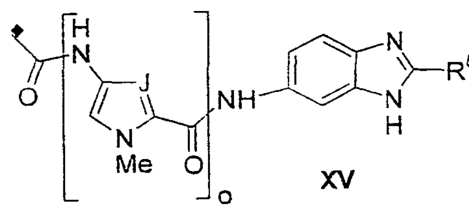
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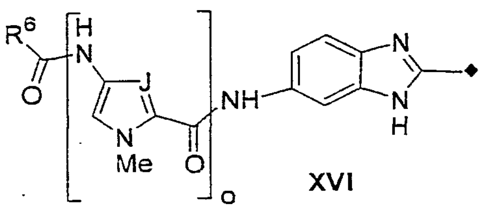

XVI

wherein in structures **XI - XVI** R^6 is independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^7 NO_2, NH_2, NHR^7, NR^7R^7, SR^7, imidazolyl, R^7-piperazinyl, morpholino, SO_2R^7, CF_3, CN, CO_2H, CO_2R^7, CHO, COR^7, $CONH_2$, $CONHR^7$, $CONR^7R^7$;

R^6 can also be represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^7, NH_2, NHR^7, NR^7R^7, SH, SR^7, imidazolyl, R^7-piperazinyl, morpholino, SO_2R^7, CF_3, CN, CO_2H, CO_2R^7, CHO, COR^7, $CONH_2$, $CONHR^7$, $CONR^7R^7$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^7 is independently selected from an optionally substituted C_{1-4} alkyl

or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR^8, NH_2, NHR^8, NR^8_2 or $N(OH)R^{98}$ wherein each R^8 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH;

D represents up to four of the following groups as substituents at any available ring carbon position; H, R^9, hydroxy, alkoxy, halogen, NO_2, NH_2, NHR^9, NR^9_2, SH, SR^9, SO_2R^9, CF_3, CN, CO_2H, CO_2R^9, CHO, COR^9, $CONH_2$, $CONHR^9$ or $CONR^9R^9$, cyclic alkylamino, imidazolyl, alkylpiperazinyl and morpholino, wherein each R^9 independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR^{10}, NH_2, NHR^{10}, NR^{10}_2 or $N(OH)R^{10}$ wherein each R^{10} is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH;

and wherein any available ring carbon position of formulae **II**- **XVI** can also be optionally replaced by –N- when the valency and configuration of the formula allows, the point of attachment of formulae **II**- **XVI** to the A group defined above is represented by ◆; and wherein in formulae **XI** and **XII**, m is selected from 2, 3 or 4,
and wherein in formulae **XI, XII, XV or XVI** J is selected from CH or N; and wherein in formulae **XIII** and **XIV** n is selected from 0, 1 or 2, and
wherein in formulae **XV** *and* **XVI** *o is selected from* 1 or 2.

A preferred embodiment of formula I′ is one in which the DNA targeting unit is selected from one of formulae III - IX.

A preferred embodiment of formula I′ is one in which D of the DNA targeting unit of Formulae II – X is H or Me.

Preferred compounds of formula I′ include the following

wherein X is O-, Y is H, A is–$(CH_2)_3NH(CH_2)_3NHCO$-, the DNA targeting unit represents formula VI and D is H;

wherein X is O-, Y is H, A is–$(CH_2)_3NMe(CH_2)_3NHCO$-, the DNA targeting unit

represents formula VI and D is H;

wherein X is O-, Y is H, A is–$(CH_2)_2NH(CH_2)_2NHCO$-, the DNA targeting unit represents formula VI and D is H;

wherein X is O-, Y is H, A is–$(CH_2)_2NMe(CH_2)_2NHCO$-, the DNA targeting unit represents formula VI and D is H;

wherein X is O-, Y is H, A is–$(CH_2)_3NH(CH_2)_3NHCO$-, the DNA targeting unit represents formula VIII and D is H;

wherein X is O-, Y is H, A is–$(CH_2)_3NMe(CH_2)_3NHCO$-, the DNA targeting unit represents formula VIII and D is H;

wherein X is O-, Y is H, A is –$(CH_2)_2NH(CH_2)_2NHCO$-, the DNA targeting unit represents formula VIII and D is H;

wherein X is O-, Y is H, A is –$(CH_2)_2NMe(CH_2)_2NHCO$-, the DNA targeting unit represents formula VIII and D is H;

wherein X is O-, Y is H, A is –$(CH_2)_3NH(CH_2)_3NHCO$-, the DNA targeting unit represents formula VIII and D is Me;

wherein X is O-, Y is H, A is –$(CH_2)_3NMe(CH_2)_3NHCO$-, the DNA targeting unit represents formula VIII and D is Me;

wherein X is O-, Y is H, A is–$(CH_2)_2NH(CH_2)_2NHCO$-, the DNA targeting unit represents formula VIII and D is Me;

wherein X is O-, Y is H, A is–$(CH_2)_2NMe(CH_2)_2NHCO$-, the DNA targeting unit represents formula VIII and D is Me;

wherein X is O-, Y is H, A is –$(CH_2)_3NH(CH_2)_3NHCO$-, the DNA targeting unit represents formula IX and D is Me;

wherein X is O-, Y is H, A is $-(CH_2)_3NMe(CH_2)_3NHCO$-, the DNA targeting unit represents formula IX and D is Me; and wherein X is O-, Y is H, A is $-(CH_2)_2NH(CH_2)_2NHCO$-, the DNA targeting unit represents formula IX and D is Me;

wherein X is O-, Y is H, A is $-(CH_2)_2NMe(CH_2)_2NHCO$-, the DNA targeting unit represents formula IX and D is Me;

In a third aspect the invention provides for the use in a method of therapy for treating cancers including the step of administering a compound of Formula I as defined above or a compound of Formula I′ as defined above or a mixture thereof in a therapeutically effective amount to tumour cells in a subject.

Preferably the tumour cells are in a hypoxic environment.

It is preferred that the method of therapy further includes the step of administering radiotherapy to the tumor cells before, during or after the administration of the compound of Formula I as defined above or a compound of Formula I′ as defined above or a mixture thereof to the tumour cells.

It is preferred that the method of therapy further includes the step of administering one or more chemotherapeutic agents to the tumor cells before, during or after the administration of the compound of Formula I as defined above or a compound of Formula I′ as defined above or a mixture thereof to the tumour cells.

While these compounds will typically be used in cancer therapy of human subjects, they can be used to target tumor cells in other warm blooded animal subjects such as other primates, farm animals such as cattle, and sports animals and pets such as horses, dogs, and cats.

A "therapeutically effective amount", is to be understood as an amount of a compound of Formula I as defined above or a compound of Formula I′ as defined above or a mixture thereof that is sufficient to show benefit to a patient. The actual amount, rate and time-

course of administration, will depend on the nature and severity of the disease being treated. Prescription of treatment is within the responsibility of general practitioners and other medical doctors.

A hypoxic environment is to be understood as either an *in vitro* or *in vivo* environment having a poorer blood supply and lower oxygen tension than normal tissues.

It is to be understood that the compound of Formula I or Formula I′ can be administered alone or in combination with other chemotherapeutic agents or treatments, especially radiotherapy, either simultaneously or sequentially dependent upon the condition to be treated.

Preferred chemotherapeutic agents can be selected from:
Cisplatin or other platinum-based derivatives,
Temozolomide or other DNA methylating agents,
Cyclophosphamide or other DNA alkylating agents,
Doxorubicin, mitoxantrone, camptothecin or other topoisomerase inhibitors,
Methotrexate, gemcitabine or other antimetabolites.

In a fourth aspect of the present invention there is provided a pharmaceutical composition including a therapeutically effective amount of a compound of formula I or compound of formula I′ or a mixture thereof, a pharmaceutically acceptable excipient, adjuvant, carrier, buffer or stabiliser.

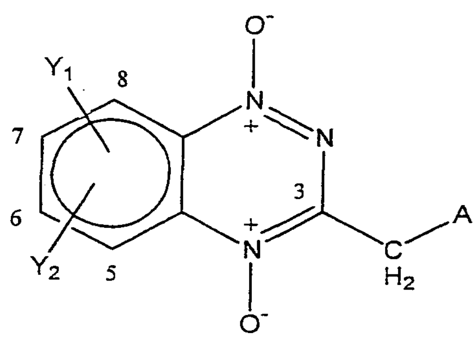
The pharmaceutically acceptable excipient, adjuvant, carrier, buffer or stabiliser should be non-toxic and should not interfere with the efficacy of the active ingredient. The precise nature of the carrier or other material will depend on the route of administration, which can be oral, or by injection, such as cutaneous, subcutaneous, or intravenous injection.

Pharmaceutical compositions for oral administration can be in tablet, capsule, powder or liquid form. A tablet may comprise a solid carrier or an adjuvent. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water,

petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included. A capsule may comprise a solid carrier such as gelatin.

For intravenous, cutaneous or subcutaneous injection, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has a suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride injection, Ringer's injection, Lactated Ringer's injection. Preservatives, stabilisers, buffers antioxidants and/or other additives may be included as required.

In a fifth aspect of the present invention there is provided a method of making a compound of formula XVII



XVII

wherein

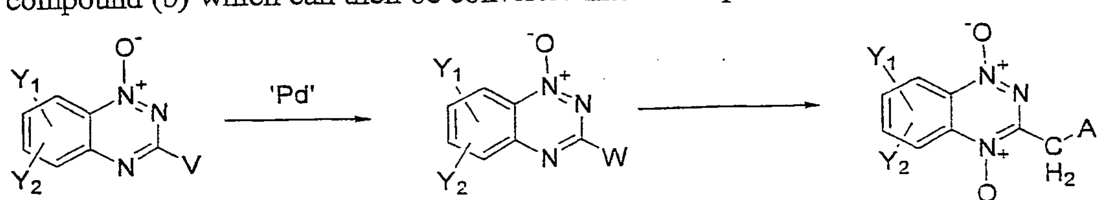
Y_1 and Y_2 at one or more of the available carbons 5-8 on the benzo ring: are each independently selected from the following groups: halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl and morpholino;

wherein each R is independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

R can also represent an optionally substituted aryl or an optionally substituted

heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S; wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2, NR^2_2 or $N(OH)R^2$ wherein each R^2 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

A represents an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^3, NR^3_2, or $N(OH)R^3$ wherein each R^3 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain is optionally interrupted by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, where each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, NR^5_2 or $N(OH)R^5$ wherein each R^5 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH;
or a pharmacologically acceptable salt thereof,
including the step of coupling a compound (a) using a palladium reagent to form compound (b) which can then be converted into a compound of XVII as defined above;

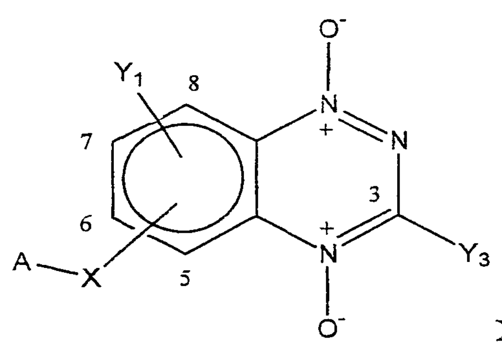


(a) (b) XVII

wherein in compound (a)
V is halogen which is selected from Cl, Br or I and Y_1, Y_2 are as defined above; and wherein in compound (b) Y_1, Y_2 are as defined above, W is selected from an optionally substituted

C_{1-12}alkyl, optionally substituted C_{2-12}alkenyl, and optionally substituted C_{2-12}alkynyl group, wherein the optional substituents is selected from halo, OH, OR^6, NO_2, NH_2, NHR^6, NR^6R^6, SH, SR^6, imidazolyl, R^6-piperazinyl, morpholino, SO_2R^6, CF_3, CN, CO_2H, CO_2R^6, CHO, COR^6, $CONH_2$, $CONHR^6$, $CONR^6R^6$, wherein each R^6 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^7, $NR^7{}_2$ or $N(OH)R^7$ wherein each R^7 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH.

In a sixth aspect of the present invention there is provided a method of making a compound of formula XVII′



XVII′

wherein Y_1 represents at one or more of the available carbons 5-8 on the benzo ring the following groups:
halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl and morpholino;

Y_3 is selected from the following groups H, R, OR, NH_2, NHR, NR_2, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl and morpholino

wherein each R of groups Y_1 and Y_3 is independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2,

NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

R can also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2 NR^2_2 or $N(OH)R^2$ wherein each $R^2$is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

wherein X represents NH, NMe, CH_2, SO, SO_2, or O;

A represents an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^3 NR^3_2 or $N(OH)R^3$ wherein each R^3 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain is optionally interrupted by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, wherein each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, NR^5_2 or $N(OH)R^5$ wherein each R^5 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and

or a pharmacologically acceptable salt thereof;

including the steps of coupling a compound (a) using a palladium reagent to form compound (b) which can then be converted into a compound of XVII' as defined above;

ART 34 AMDT

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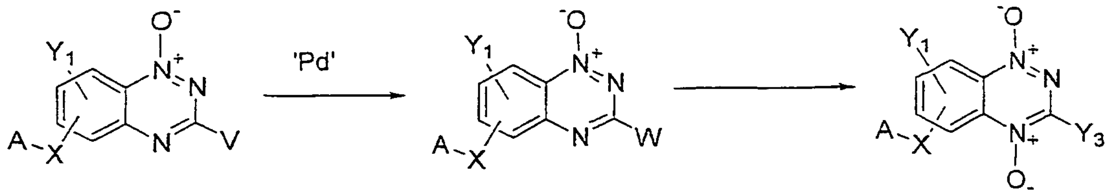


(a) (b) XVII'

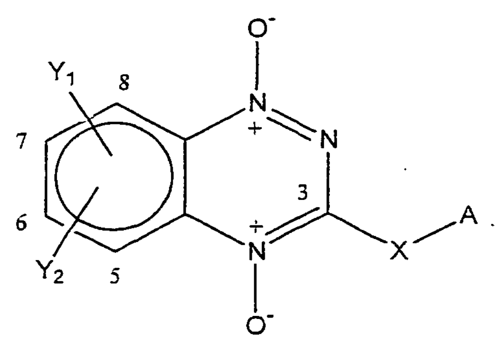
wherein in compound (a)

V is halogen which is selected from Cl, Br or I; Y_1, X and A are as defined above;

and wherein in compound (b) Y_1, X and A are as defined above,

W is selected from an optionally substituted C_{1-12}alkyl, optionally substituted C_{2-12}alkenyl, and optionally substituted C_{2-12}alkynyl group, wherein the optional substituents is selected from halo, OH, OR^6, NO_2, NH_2, NHR^6, NR^6R^6, SH, SR^6, imidazolyl, R^6-piperazinyl, morpholino, SO_2R^6, CF_3, CN, CO_2H, CO_2R^6, CHO, COR^6, $CONH_2$, $CONHR^6$, $CONR^6R^6$, wherein each R^6 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^7, NR^7_2 or $N(OH)R^7$ wherein each R^7 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH.

In a seventh aspect of the present invention there is provided a compound of formula XVIII



XVIII

wherein

Y_1 and Y_2 at one or more of the available carbons 5-8 on the benzo ring: are each independently selected from the following groups: halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl and morpholino;

wherein each R is independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

R can also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

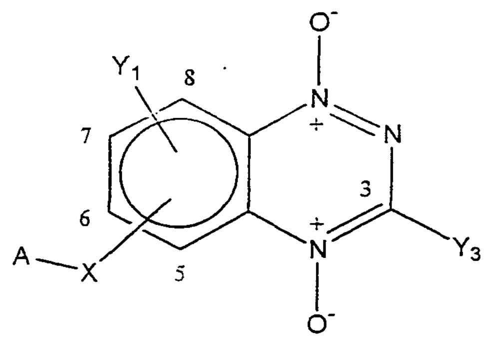
wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2, NR^2_2 or $N(OH)R^2$ wherein each R^2 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

wherein X represents NH, NMe, CH_2, SO, SO_2, or O;

A represents an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^3, NR^3_2, or $N(OH)R^3$ wherein each R^3 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain is optionally interrupted by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, where each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, NR^5_2 or $N(OH)R^5$ wherein each R^5 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH;
or a pharmacologically acceptable salt thereof.

In an eighth aspect of the present invention there is provided a compound of formula

XVII'



XVII'

wherein

Y_1 represents at one or more of the available carbons 5-8 on the benzo ring the following groups:

halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl and morpholino;

Y_3 is selected from the following groups H, R, OR, NH_2, NHR, NR_2, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl and morpholino

wherein each R of groups Y_1 and Y_3 is independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

R can also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2, $NR^2{}_2$ or $N(OH)R^2$

wherein each R^2 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

wherein X can represent NH, NMe, CH_2, SO, SO_2, or O;

A can represent an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^3, $NR^3{}_2$ or $N(OH)R^3$ wherein each R^3 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain is optionally interrupted by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, where each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, $NR^5{}_2$ or $N(OH)R^5$ wherein each R^5 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and

wherein X represents NH, NMe, CH_2, SO, SO_2, or O;

or a pharmacologically acceptable salt thereof.

In a ninth aspect of the present invention there is provided a method of making a compound of Formula I defined above including the steps of

1 preparing a compound of Formula XVIII as defined above
2 coupling the compound of Formula XVIII with a DNA targeting agent as defined above to provide a compound of Formula I.

In a tenth aspect of the present invention there is provided a method of making a compound of Formula I′ defined above including the steps of

1 preparing a compound of Formula XVII′ as defined above
2 coupling the compound of Formula XVII′ with a DNA targeting agent as defined above to provide a compound of Formula I′.

It is to be recognised that certain compounds of the present invention may exist in one or more different enantiomeric or diastereomeric forms. It is to be understood that the enantiomeric or diasteriomeric forms are included in the above aspects of the invention.

The term halo or halogen group used throughout the specification is to be taken as meaning a fluoro, chloro, bromo or iodo group.

The term pharmaceutically acceptable salt used throughout the specification is to be taken as meaning any acid or base derived salts formed from hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic, isoethonic acids and the like and potassium carbonate sodium or potassium hydroxide ammonia, triethylamine, triethanolamine and the like.

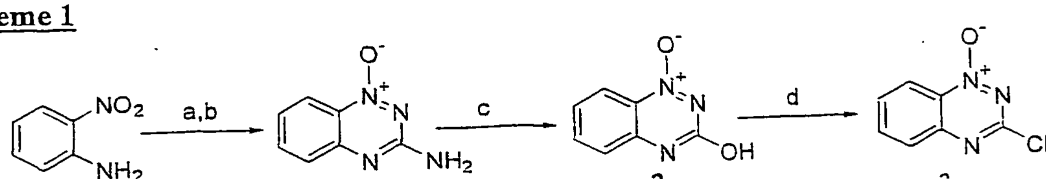
Further aspects of the present invention will become apparent from the following description given by way of example only and with reference to the accompanying synthetic schemes.

DETAILED DESCRIPTION OF THE INVENTION

Methods for preparing compounds of Formula I of the invention.

3-Chloro-1,2,4-benzotriazine 1-oxide (**3**) was readily synthesised from 2-nitroaniline in 3 steps (50% yield) (Scheme 1). Preparation of the diamine **4** can be achieved as shown in Scheme 2. Coupling of chloride **3** with the monoprotected diamine **4**, readily prepared in 85% yield from the 6-aminohexan-1-ol, gave carbamate **5** as illustrated in Scheme 3. Reaction of **5** with MCPBA in DCM gives 1,4-dioxide **6** in 39% yield and recovered starting material **5** (50%). This represents a departure from known methods (Lee et al, US Patent 5616584, April, 1997) that use trifluoroperacetic acid as the oxidant. Cleavage of the 1,4-dioxide carbamate **6** with HCl in MeOH gave 1,4-dioxide **7** in good yield.

Scheme 1



1 2 3

Reagents: (yield %)

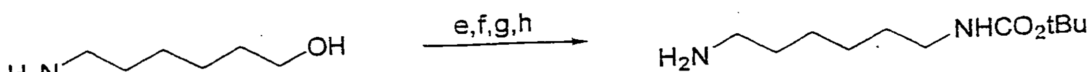
a) NH_2CN, HOAc, HCl;

b) NaOH;

c) HCl, $NaNO_2$, 49% from nitroaniline;

d) $POCl_3$, $PhNMe_2$, 59%

Scheme 2



4

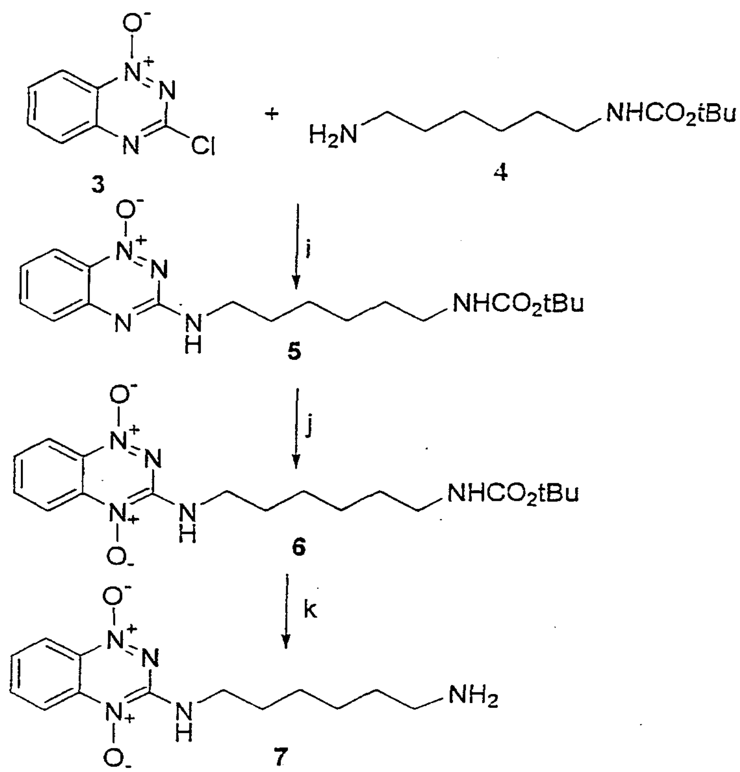
Reagents:

e) BOC_2O, DCM;

f) MsCl, Et_3N, DCM;

g) NaN_3, DMF.

Scheme 3



Reagents: (yield %)

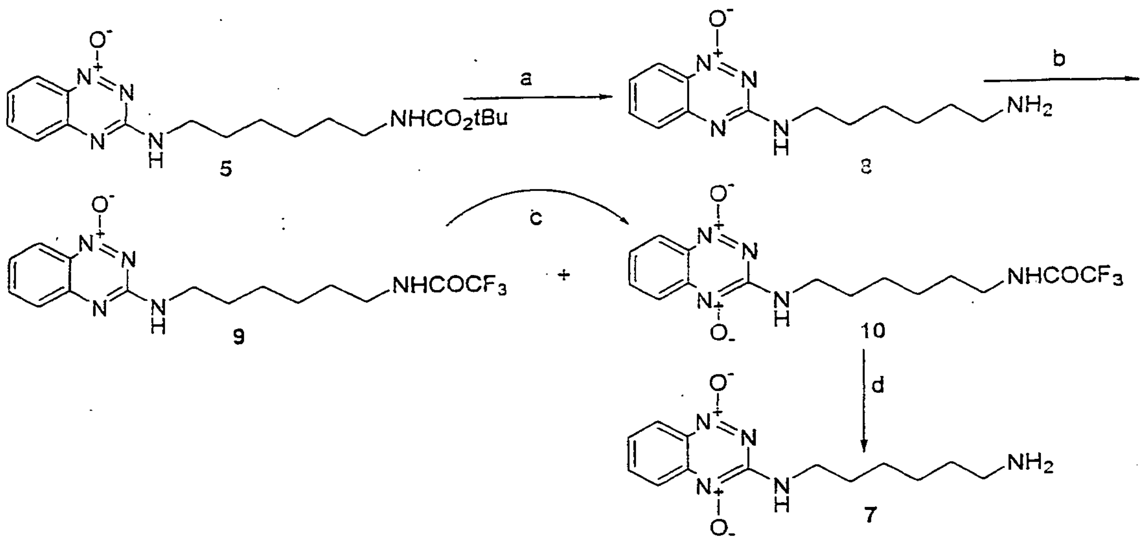
i) Et_3N, DCM, 65%;

j) MCPBA, DCM, 37% + 50% SM;

k) HCl, MeOH, 85%

An alternative approach to using trifluoroacetic anhydride to provide protection for the primary amine and to generate trifluoroperacetic acid *in situ* was also used (Scheme 4). Deprotection of carbamate **5** gave the amine **8**. Reaction of **8** with trifluoroacetic anhydride followed by 30% H_2O_2 gave a mixture of the 1-oxide **9** (22% yield) and 1,4-dioxide **10** (51% yield). 1-Oxide **9** was oxidised with trifluoroperacetic acid to give **10** (29% yield) as well as starting material **9** (61% yield). Deprotection of the trifluoroacetamide **10** provided 1,4-dioxide **7** in good yield.

Scheme 4



Reagents: (yield %)

a) HCl, MeOH, 87%;

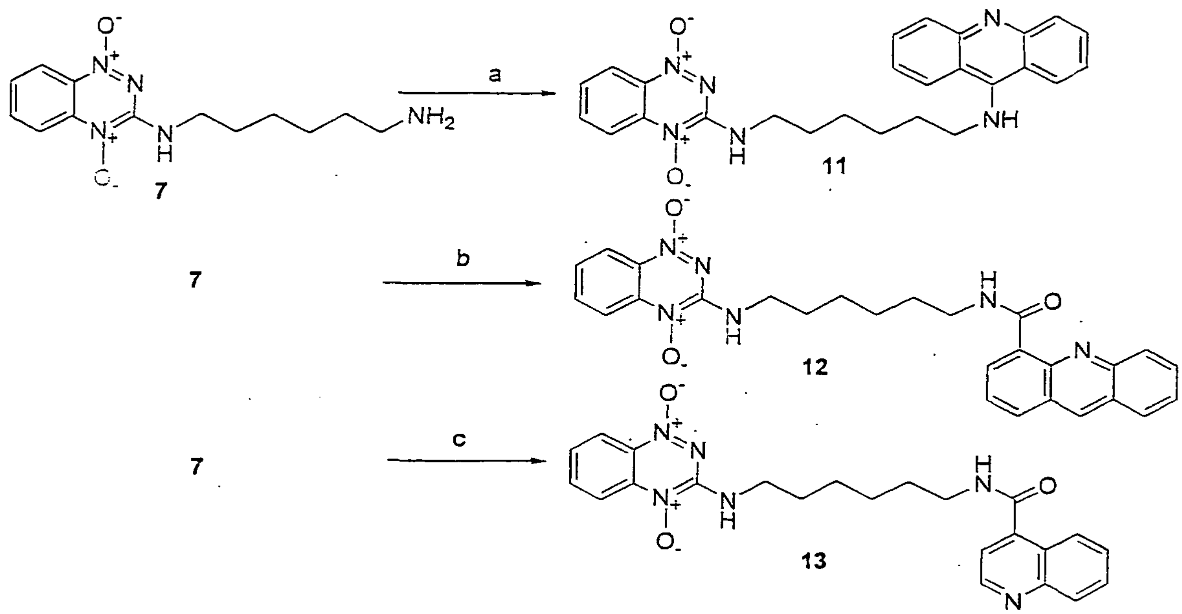
b) $(CF_3CO)_2O$, 35% H_2O_2, DCM, 51% + 10 (22%);

c) CF_3CO_3H, DCM, 29% + SM (61%);

d) NaOH, MeOH, 83%.

Coupling of 1,4 dioxide **7** with 9-methoxyacridine (Albert, "The Acridines" 2nd ed. 1966, Edward Arnold, London, p. 281) provided a compound of Formula I: the aminoacridine derivative **11** (Scheme 5). Similarly, reaction of 7 with 4-(1*H*-imidazol-1-ylcarbonyl)acridine (Spicer et al., *Anti-Cancer Drug Des.*, **1999**, 14, 281-289) gave **12**, a compound of Formula I. Similarly, reaction of the imidazolide of quinoline 4-acetic acid gave **13**, a compound of Formula I.

Scheme 5



Reagents: (yield %)

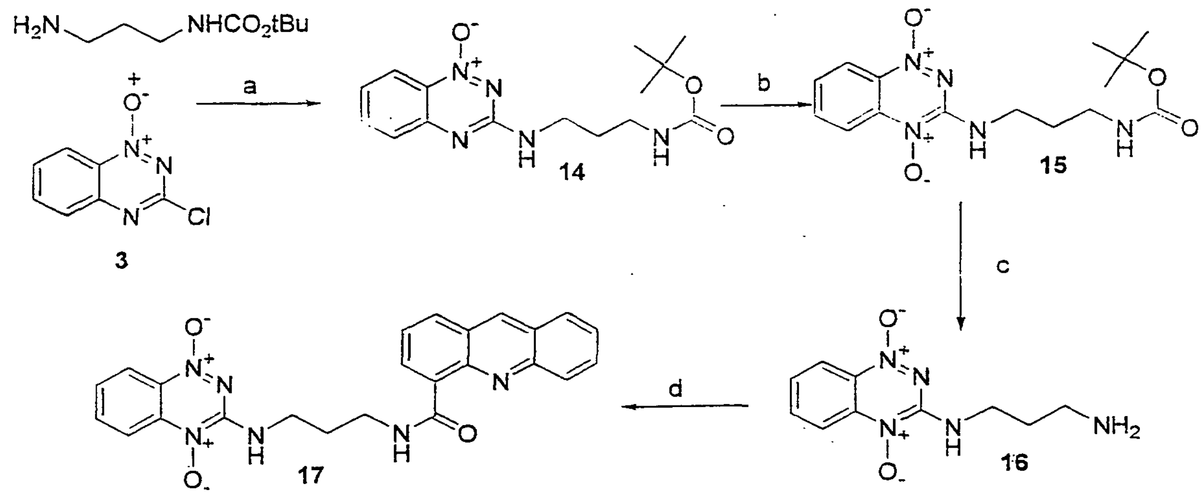
a) 9-methoxyacridine, MeOH, 60%;

b) acridine 4-carboxylic acid, CDI, DMF; **7**, THF, 91%;

c) quinoline 4-carboxylic acid, CDI, DMF, 80%; **7**, DMF/THF.

Reaction of chloride **3** with tert-butyl 3-aminopropylcarbamate gives **14**, which was oxidised to 1,4-dioxide **15** with MCPBA (Scheme 6). Deprotection of **15** under acid conditions gave amine **16** which was reacted with 4-(1*H*-imidazol-1-ylcarbonyl)acridine to give **17**, a compound of Formula I.

Scheme 6



Reagents: (yield %)

a) Et_3N, DCM, 74%;

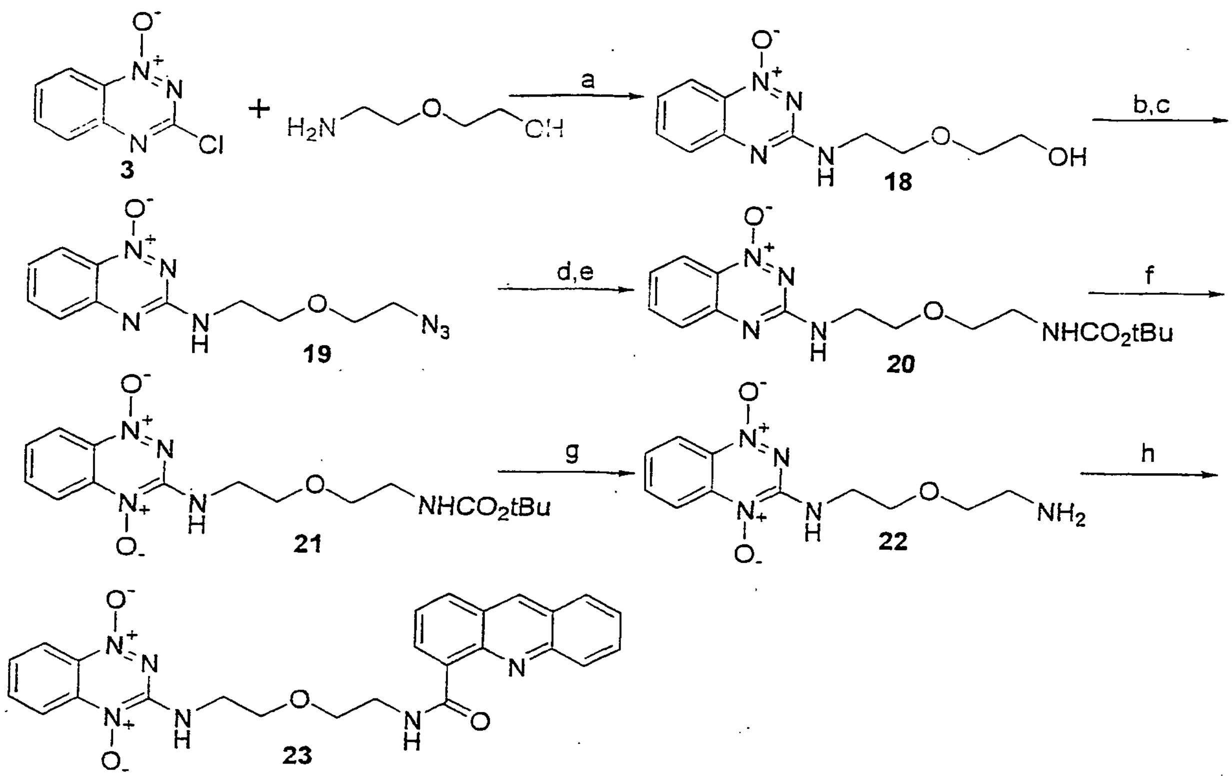
b) MCPBA, DCM, 24% + 45% SM ;

c) HCl, MeOH, 80%;

d) acridine 4-carboxylic acid, CDI, DMF; **16**, DCM, 80%.

Coupling of chloride **3** with 2-(aminoethoxy)ethanol gave alcohol **18** in 63% yield which was converted to the mesylate and displaced with sodium azide to give azide **19** in 89% yield (Scheme 7). Selective reduction of the azide group rather than 1-oxide of **19** could not be effected by hydrogenation using palladium on charcoal or Lindlar catalyst (Rolla et al., *J. Org. Chem.*, **1965**, 47, 4322-432). Other methods for reducing azides such as $NaBH_4$ under PTC (Corey et al., *Synth.*, **1975**, 590-591), BH_3.DMS (Hassner & Levy, *J. Amer. Chem. Soc.*, **1965**, 87, 4203-4204) or Staudinger conditions using $P(OEt)_3$ (Koziara & Zwierzak, *Synth.*, **1992**, 1063-1065) were ineffective. However, treatment of azide **19** with propane-1,3-dithiol and Et_3N in refluxing methanol (Bayley et al., *Tet. Lett.*, **1978**, 39, 3633-3634) provided the intermediate amine which was protected without isolation with di-*tert*-butyldicarbonate to give carbamate **20** in 93% yield for the two steps. Oxidation of **20** with MCPBA gave 1,4-dioxide **21** in 40% yield as well as recovered starting material (50%). Deprotection of **21** with trifluoroacetic acid gave amine **22** in 91% yield. Coupling of **22** with 4-(1*H*-imidazol-1-ylcarbonyl)acridine gave compound **23** in 97% yield.

Scheme 7



Reagents: (yield %)

a) Et_3N, DCM, 63%;

b) MsCl, Et_3N, DCM;

c) NaN_3, DMF, 89% from 24;

d) propane-1,3-dithiol, Et_3N, MeOH;

e) BOC_2O, THF, 93% from 25;

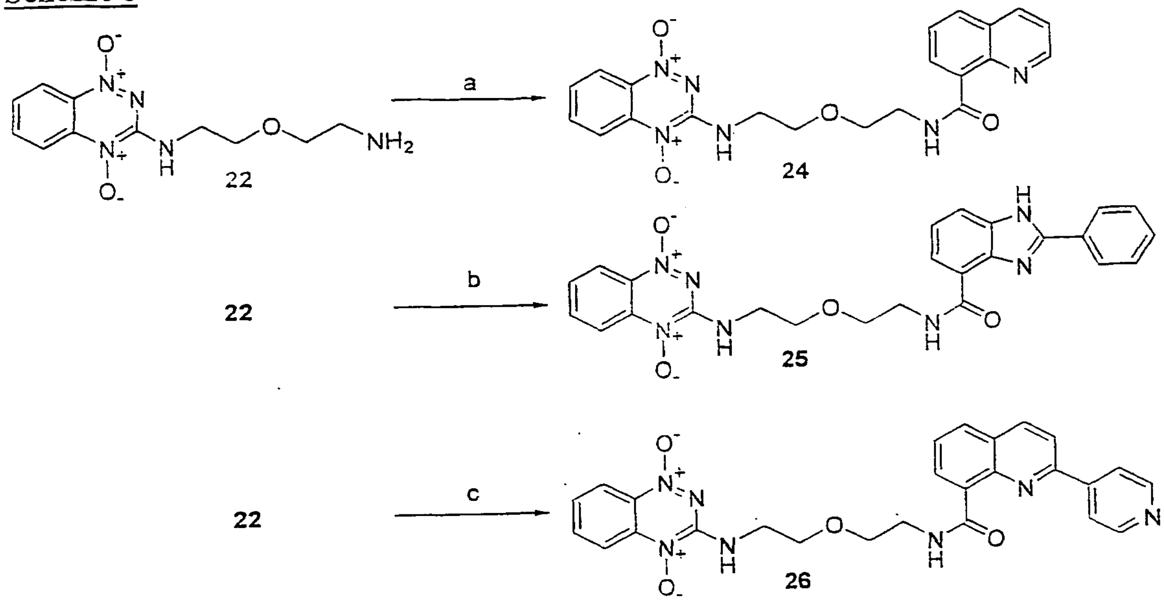
f) MCPBA, $NaHCO_3$, DCM, 40% + 50% SM;

g) CF_3CO_2H, DCM, 91%;

h) acridine 4-carboxylic acid, CDI, DMF; 28, THF, 97%.

Similarly, reaction of **22** with the imidazolides of 8-quinolinecarboxylic acid, 2-phenyl-1*H*-benzimidazole-4-carboxylic acid (Denny et al., *J. Med. Chem.* **1990**, 33, 814-819) and 2-(4-pyridinyl)-8-quinolinecarboxylic acid (Atwell et al., *J. Med. Chem.* **1989**, 32, 396-401) gave compounds of Formula I: **24**, **25**, and **26** respectively (Scheme 8).

Scheme 8



Reagents:

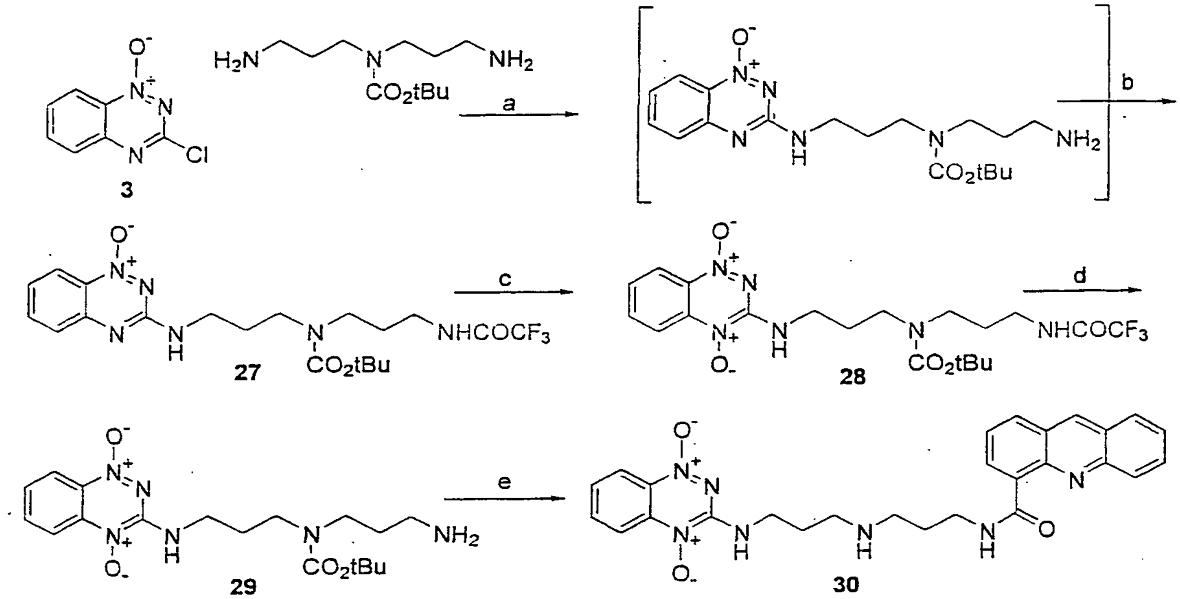
a) quinoline 8-carboxylic acid, CDI, DMF; **22**, DCM, 84%;

b) 2-phenylbenzimidaole 4-carboxylic acid, CDI, DMF; **22**, DCM, 86%;

c) 2-pyridylquinoline 8-carboxylic acid, CDI, DMF; **22**, DCM, 70%.

Reaction of chloride **3** with *tert*-butyl bis(3-aminopropyl)carbamate and protection of the intermediate primary amine with trifluoroacetic anhydride gave the trifluoroacetamide **27** in 39% for the two steps (Scheme 9). Oxidation of **27** with MCPBA gave the 1,4-dioxide **28** (8% with 65% recovered starting material). Deprotection of **28** gave amine **29** in good yield which was coupled to 4-(1*H*-imidazol-1-ylcarbonyl)acridine to give compound **30**, a compound of Formula I.

Scheme 9



Reagents: (yield %)

a) Et_3N, DCM;

b) $(CF_3CO)_2O$, DCM, 22% from **3**;

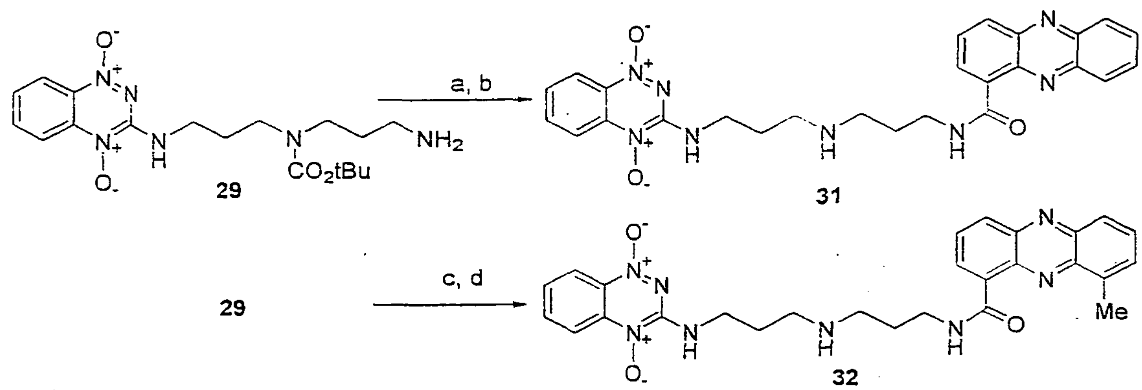
c) MCPBA, $NaHCO_3$, DCM, 8% + 65% SM;

d) K_2CO_3, MeOH, H_2O, 74%;

e) acridine 4-carboxylic acid, CDI, DMF; **30**, DCM, 67%; HCl, MeOH, 90%.

Similarly, reaction of amine **29** with imidazolides of phenazine and 9-methylphenazine followed by deprotection under acidic conditions gave compounds **31** and **32**, respectively (Scheme 10).

Scheme 10



Reagents: (yield %)

a) phenazine 1-carboxylic acid, CDI, DMF; **29**, DCM, 40%.

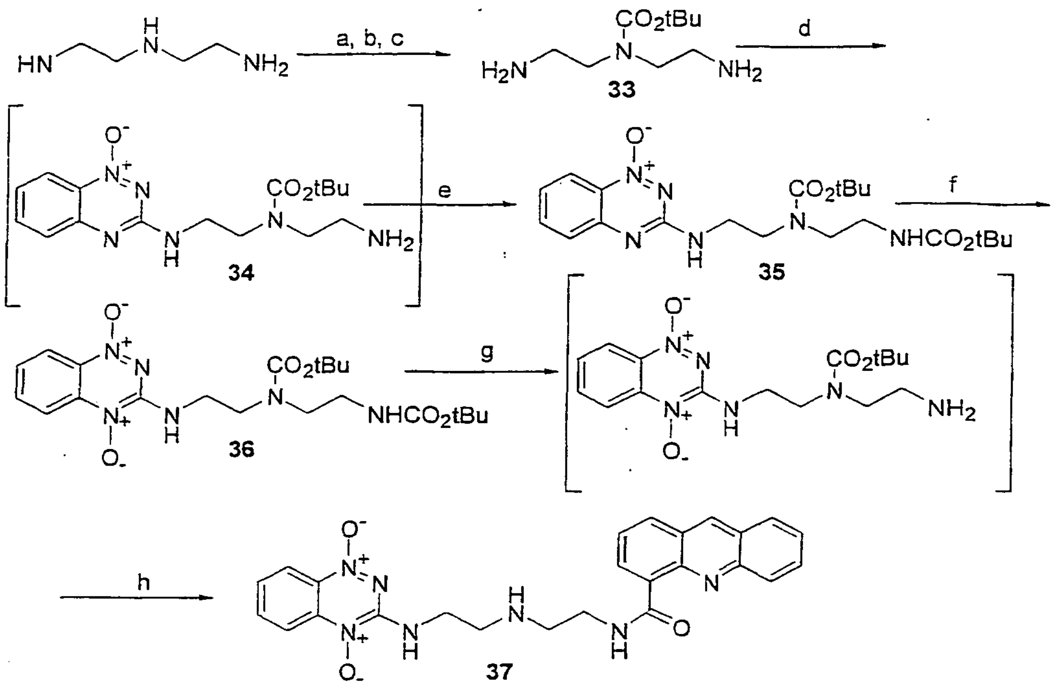
b) HCl, MeOH, 85%.

c) 9-methylphenazine 1-carboxylic acid, CDI, DMF; **29**, DCM, 40%.

d) HCl, MeOH, 86%.

Reaction of chloride **3** with amine **33**, prepared from N^1-(2-aminoethyl)-1,2-ethanediamine gave the 1-oxide **34** (Scheme 11). Compound **34** was protected as carbamate **35** and oxidized with MCPBA to give dioxide **36**. Deprotection and coupling of the intermediate amine with the imidazolide of acridine 4-carboxylic acid gave compound **37**, a compound of Formula I.

Scheme 11



Reagents: (yield %)

a) CF_3CO_2Et, ether, 61%;

b) $(BOC)_2O$, quant;

c) aq. NH_3, MeOH, quant;

d) **3**, Et_3N, DME, 72%;

e) $(BOC)_2O$, DCM, 52%;

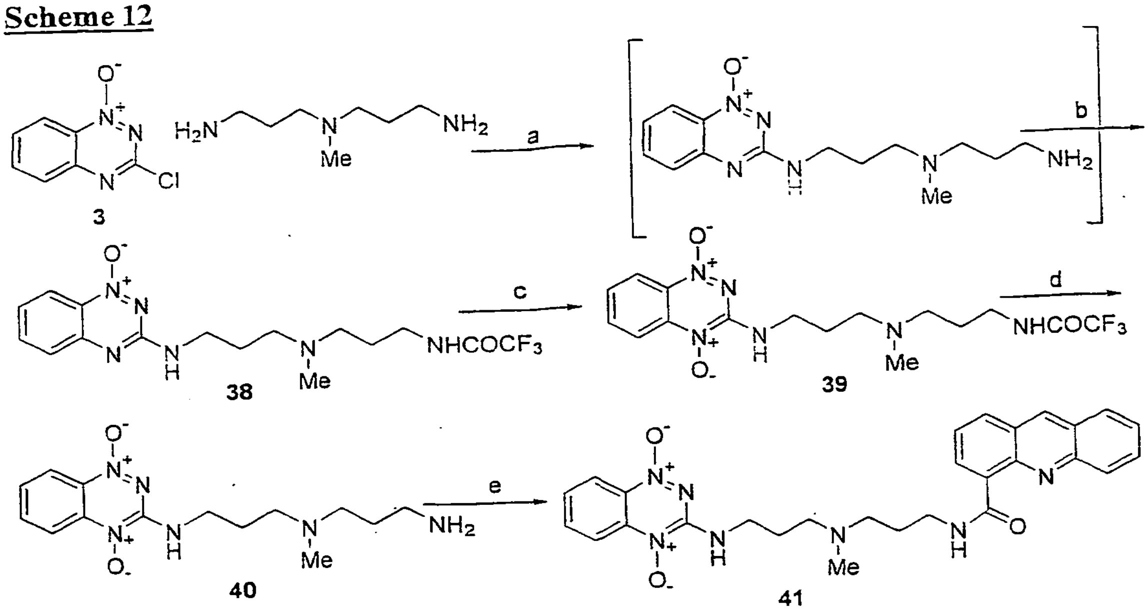
f) MCPBA, DCM, 39% + 62% SM;

g) HCl, MeOH, 76%;

h) acridine-4-carboxylic acid, CDI, DMF, 99%.

Reaction of chloride **3** with N^1-(3-aminopropyl)-N^1-methyl-1,3-propanediamine and protection of the intermediate amine gave acetamide **38** in 43% yield (Scheme 12). Oxidation of **38** with trifluoroperacetic acid under acidic conditions resulted in selective aromatic N-oxidation to give 1,4-dioxide **39** (27%) and recovered starting material **38** (24%). Deprotection of **39** gave amine **40** which was coupled with 4-(1*H*-imidazol-1-ylcarbonyl)acridine to give compound **41**, a compound of Formula I, in 66% yield.

Scheme 12



Reagents: (yield %)

a) Et_3N, DCM;

b) $(CF_3CO)_2O$, DCM, 43% from **3**;

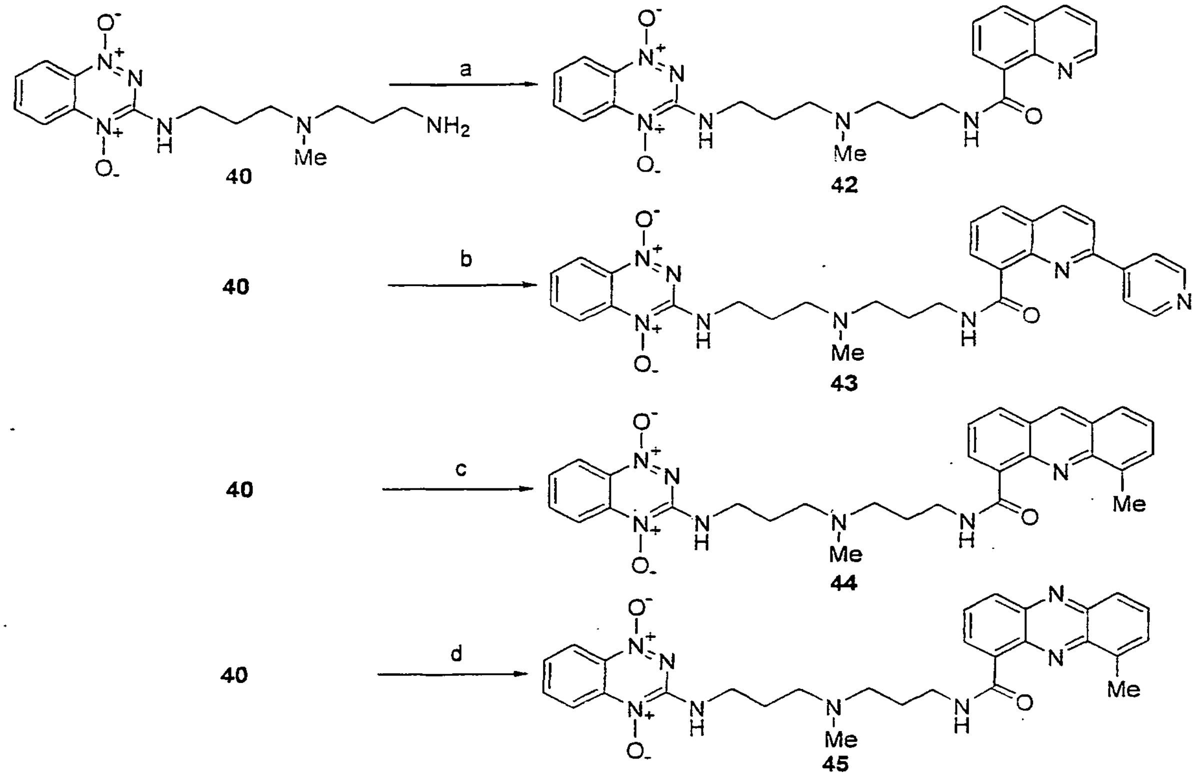
c) MCPBA, $NaHCO_3$, DCM, 27% + 24% SM;

d) NH_4OH, MeOH, quant.;

e) acridine 4-carboxylic acid, CDI, DMF; **40**, DCM, 66%.

Similarly, reaction of **40** with the imidazolides of 8-quinolinecarboxylic acid, 2-(4-pyridinyl)-8-quinolinecarboxylic acid (Atwell et al., *J. Med. Chem.* **1989**, 32, 396-401), 5-methyl-4-acridine carboxylic acid, and 9-methyl-4-phenazinecarboxylic acid gave compounds **42**, **43**, **44**, and **45** respectively (Scheme 13).

Scheme 13



Reagents: (yield %)

a) quinoline 8-carboxylic acid, CDI, DMF; **40**, DCM, 91%;

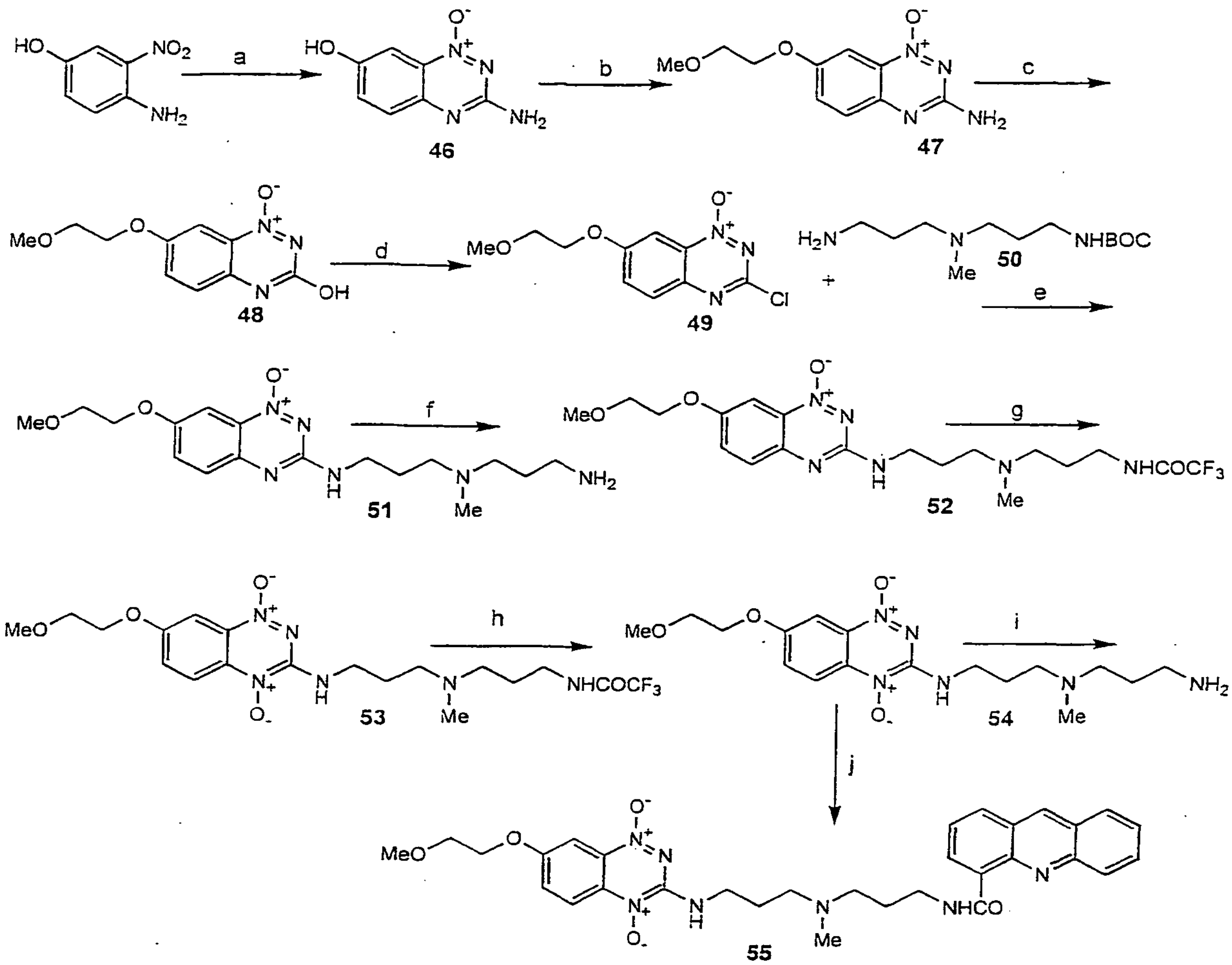
b) 2-pyridylquinoline 8-carboxylic acid, CDI, DMF; **40**, DCM, 94%;

c) 5-methylacridine-4-carboxylic acid, CDI, DMF; **40**, DCM, 88%;

d) 9-methylphenazine-4-carboxylic acid, CDI, DMF; **40**, DCM, 90%.

Reaction of 4-amino-3-nitrophenol with cyanamide under acidic conditions followed by condensation under basic conditions gave the phenol **46** (Friebe et. al. US Patent 5,856,325, Jan 5, 1999), which was alkylated under basic conditions to give ether **47** (Scheme 14). Diazotization of **47** gave **48**, which was chlorinated with $POCl_3$ to give chloride **49**. Coupling of chloride **49** with amine **50** gave the 1-oxide **51**. Protection of **51** as the trifluoroacetamide **52** and oxidation with trifluoroperacetic acid gave the dioxide **53**. Deprotection of **53** gave intermediate amine **54**, which was coupled with the imidazolide of acridine-4-carboxylic acid to give compound **55**, a compound of Formula I.

Scheme 14



Reagents: (yield %)

a) NH_2CN, HCl; NaOH, 97%;

b) $MeOCH_2CH_2Br$, K_2CO_3, DMF, 77%;

c) $NaNO_2$, HCl, 68%;

d) $POCl_3$, 83%;

e) Et_3N, DME, 98%;

f) CF_3CO_2Et, H_2O, MeCN, 87%;

g) CF_3CO_3H, DCM, 30%;

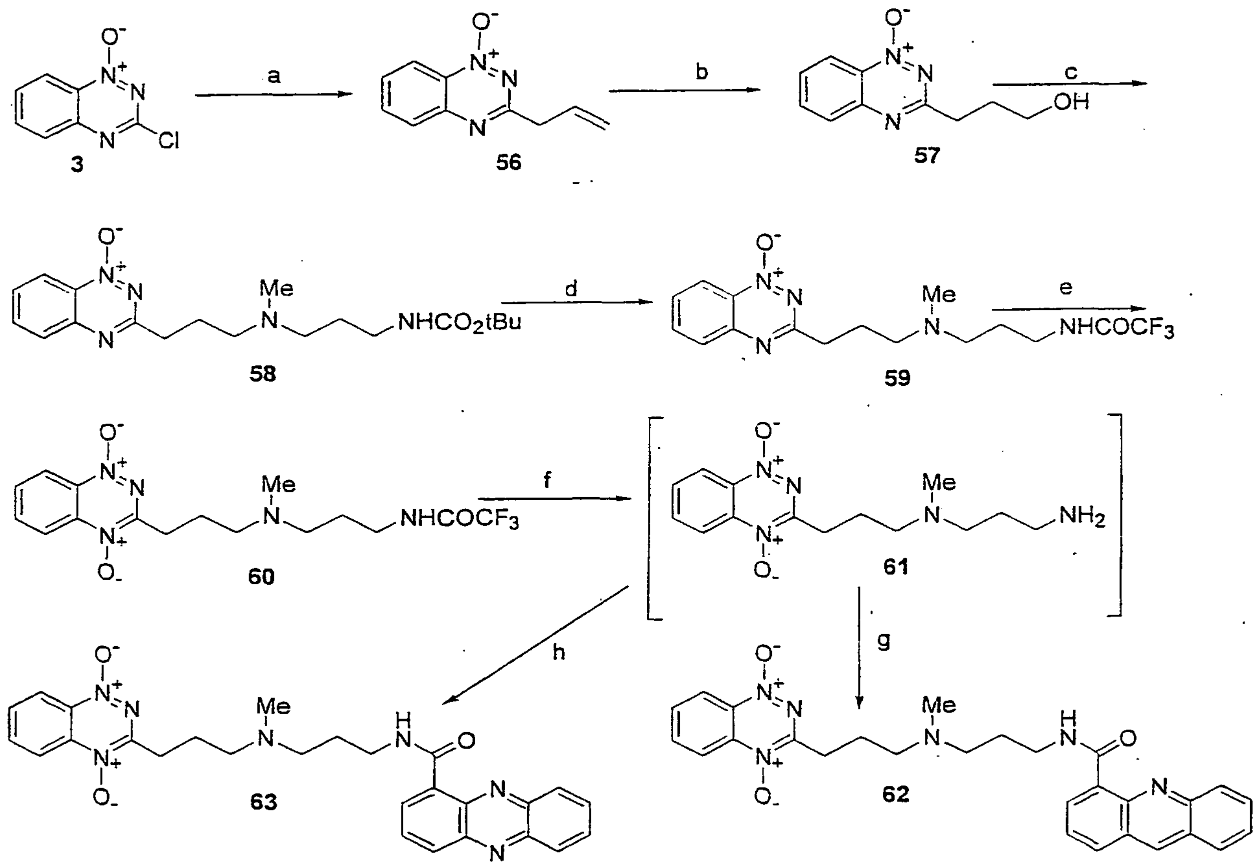
h) aq. NH_3, MeOH;

i) acridine-4-carboxylic acid, CDI; DMF; 54, THF, 79% (two steps).

Reaction of chloride **3** with allyltributyltin in the presence of tetrakis-palladiumtriphenylphosphine in DME at reflux temperature gave alkene **56** in high yield (Scheme 15). Hydroboration of **56** gave the alcohol **57** which was activated with

methanesulfonyl chloride and reacted with *tert*-butyl 3-aminopropylcarbamate to give the amine **58**. Conversion to the trifluoroacetamide **59** and oxidation with trifluoroperacetic acid gave the 1,4-dioxide **60**, which was deprotected under basic conditions to give amine **61**. Coupling of amine **61** with the imidazolide of acridine-4-carboxylic acid gave compound **62**, a compound of Formula I. Similarly, coupling of amine **61** with the imidazolide of phenazine-4-carboxylic acid gave compound **63**, a compound of Formula I.

Scheme 15



Reagents: (yield %)

a) allylSnBu$_3$, Pd(PPh$_3$)$_4$, DME, 93%;

b) 9-BBN, THF; 30% H_2O_2, 3 M NaOH, 87%;

c) MsCl, Et_3N, DCM; *tert*-butyl 3-aminopropylcarbamate, DMF, 48%;

d) HCl, MeOH; CF_3CO_2Et, H_2O, MeCN, 92%;

e) CF_3CO_3H, CF_3CO_2H, $CHCl_3$, 57%;

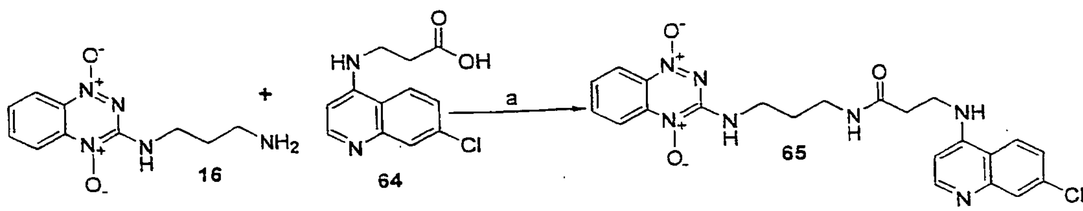
f) aq. NH_3, MeOH;

g) acridine-4-carboxylic acid, CDI, DMF; **61**, THF, 40% (two steps);

h) phenazine-1-carboxylic acid, CDI, DMF; **61**, THF, 56% (two steps).

Reaction of amine **16** with the imidazolide of *N*-(7-chloro-4-quinolinyl)-β-alanine (**64**) (Titus et al, *J. Org. Chem.*, **1948**, *13*, 39-62) gave amide **65**, a compound of Formula I (Scheme 16).

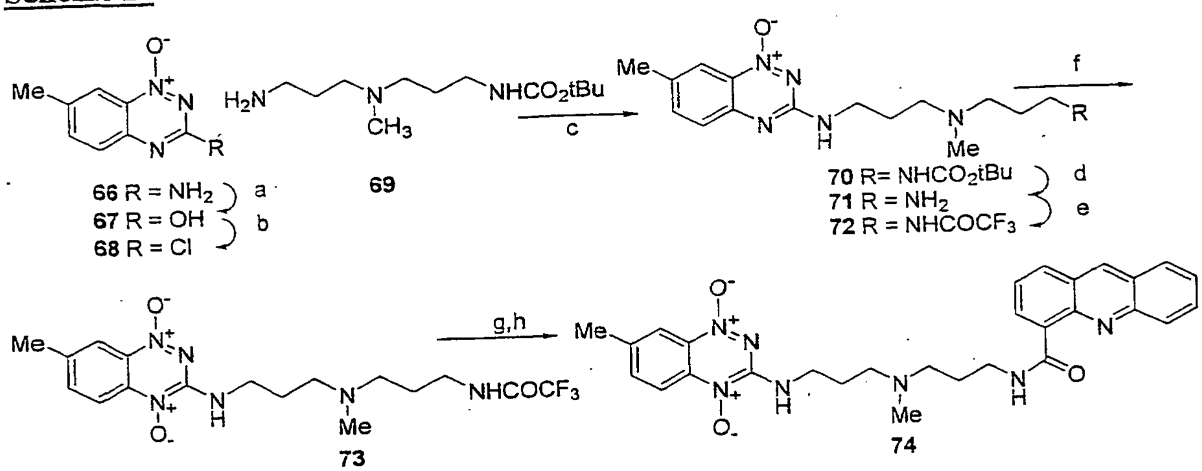
Scheme 16



Reagents: (yield %)

a) *N*-(7-chloro-4-quinolinyl)-β-alanine, CDI, DMF; **16**, DMF, 46%.

Scheme 17



Reagents: (yield %)

a) $NaNO_2$, trifluoroacetic acid, 100%;

b) $POCl_3$, 60%;

c) **68** + **69**, Et_3N, DME, 93%;

d) HCl, MeOH, 100%;

e) CF_3CO_2Et, H_2O, MeCN, 92%;

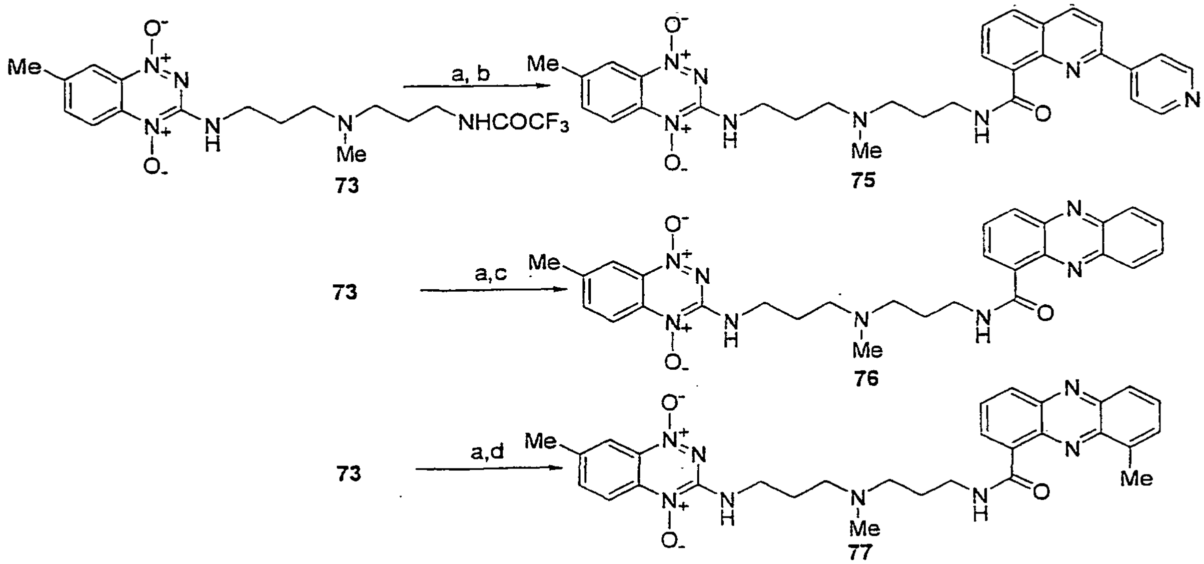
f) CF_3CO_3H, trifluoroacetic acid, DCM, 35% + 40% SM;

g) aqueous NH_3, MeOH;

h) Acridine-4-carboxylic acid, CDI, DMF, 100%.

Similarly, deprotection of 73 and reaction with the imidazolides of 2-(4-pyridinyl)-8-quinolinecarboxylic acid (Atwell et al., *J. Med. Chem.* **1989**, 32, 396-401), phenazine-1-carboxylic acid (Rewcastle et al., *J. Med. Chem.* **1987**, *30*, 843–851) and 9-methylphenazine-1-carboxylic acid (Rewcastle et al., *J. Med. Chem.* **1987**, *30*, 843–851) gave compounds of Formula I: **75**, **76**, and 77 respectively (Scheme 18).

<u>**Scheme 18**</u>



Reagents: (yield %)

a) aqueous NH_3, MeOH;

b) 2-(4-pyridyl)quinoline-8-carboxylic acid, CDI, DMF, 89%;

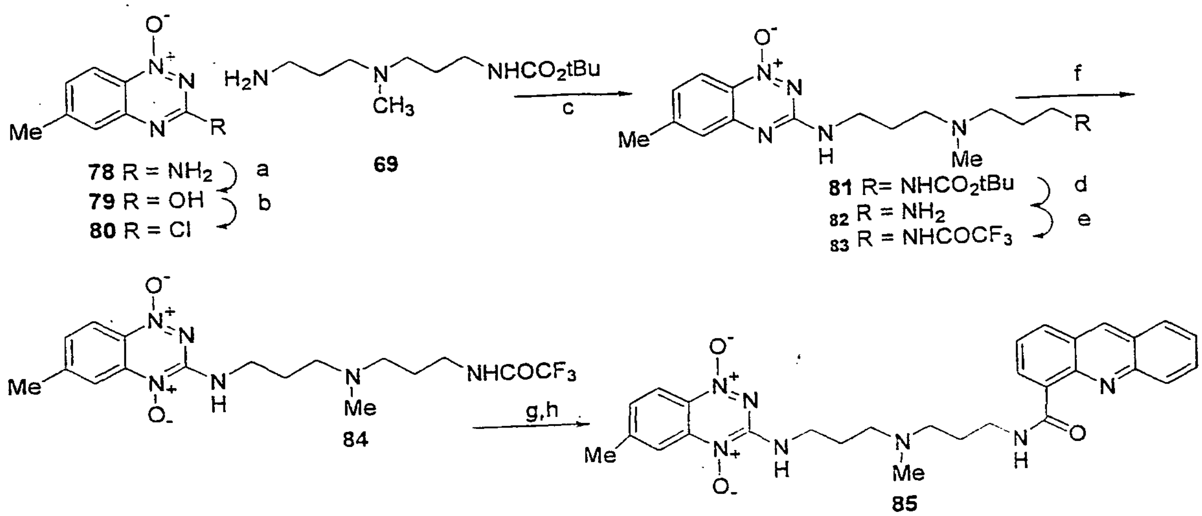
c) phenazine-1-carboxylic acid, CDI, DMF, 100%;

d) 9-methylphenazine-1-carboxylic acid, CDI, DMF, 91%.

Diazotization of amine **78** [Hay et al, *J. Med. Chem.* **2003**, 46, 169–182] with sodium nitrite in trifluoroacetic acid gave the alcohol **79** (Scheme 19) which was converted to chloride **80** in $POCl_3$. Coupling of chloride **80** with the mono-protected amine **69** gave carbamate **81** which was deprotected under acidic conditions to give amine **82** which was reprotected as the trifluoroacetate **83**. Oxidation of **83** with trifluoroperacetic acid

gave 1,4-dioxide **84** which was deprotected under basic conditions and coupled to the imidazolide of acridine-4-carboxylic acid (Spicer et al., *Anti-Cancer Drug Des.*, **1999**, 14, 281-289) to give compound **85**.

Scheme 19



Reagents: (yield %)

a) $NaNO_2$, trifluoroacetic acid, 97%;

b) $POCl_3$, 79%;

c) **69**, Et_3N, DME, 80%;

d) HCl, MeOH, 99%;

e) CF_3CO_2Et, H_2O, MeCN, 100%;

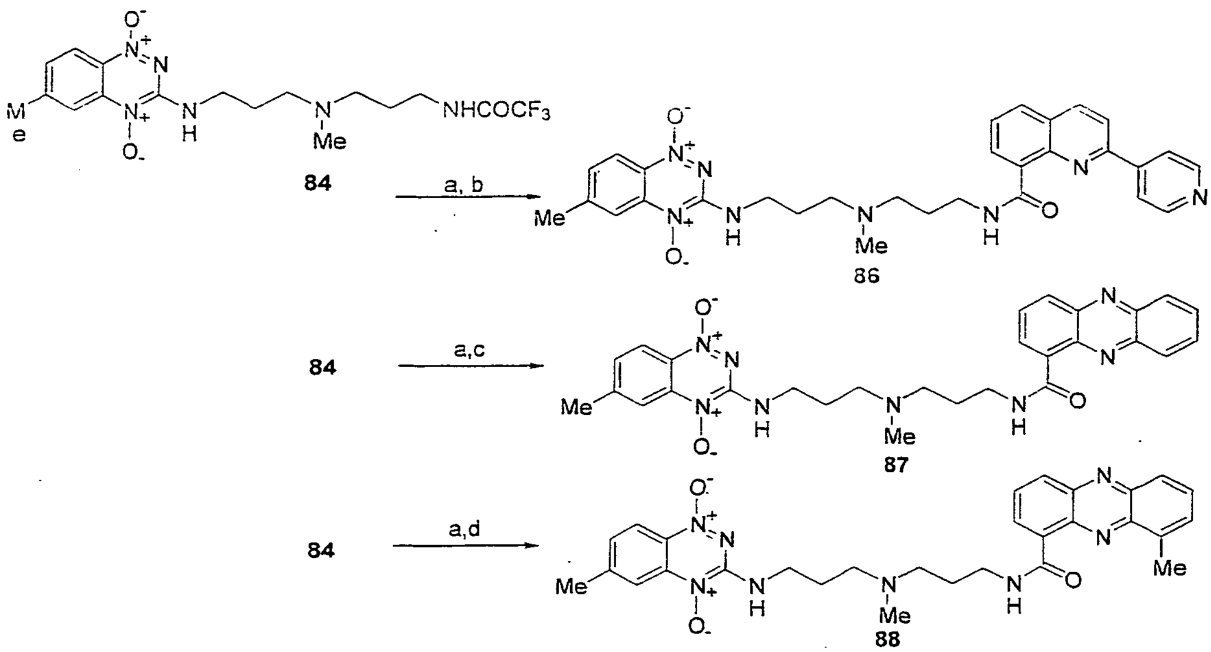
f) CF_3CO_3H, trifluoroacetic acid, DCM, 30% + 49% SM;

g) aqueous NH_3, MeOH;

h) acridine-4-carboxylic acid, CDI, DMF, 94%.

Similarly, deprotection of **84** and reaction with the imidazolides of 2-(4-pyridinyl)-8-quinolinecarboxylic acid, phenazine-1-carboxylic acid and 9-methylphenazine-1-carboxylic acid gave compounds of Formula I: **86**, **87**, and **88** respectively (Scheme 20).

Scheme 20



Reagents: (yield %)

a) aqueous NH_3, MeOH;

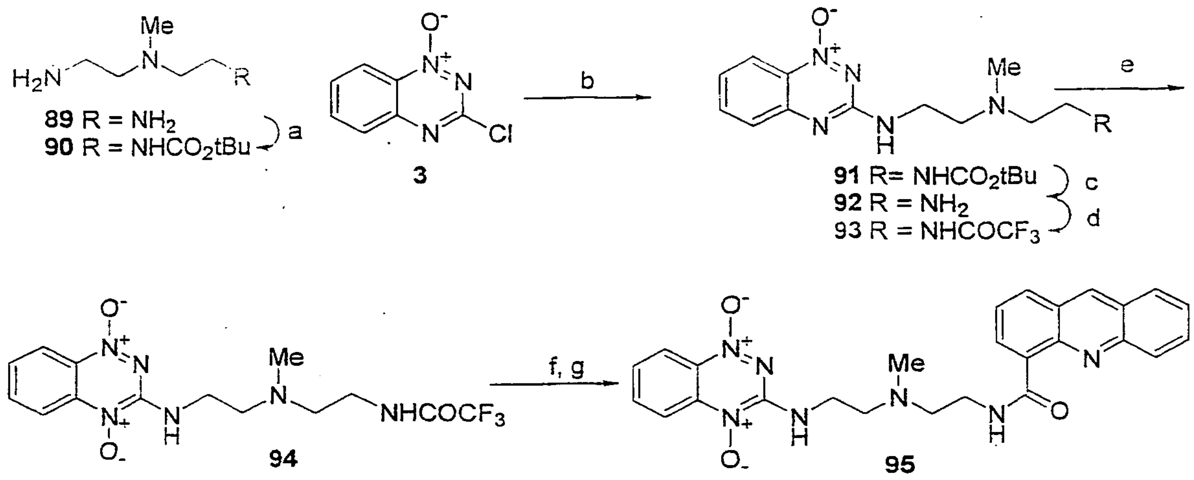
b) 2-(4-pyridyl)quinoline-8-carboxylic acid, CDI, DMF, 100%;

c) phenazine-1-carboxylic acid, CDI, DMF, 98%;

d) 9-methylphenazine-1-carboxylic acid, CDI, DMF, 91%.

Coupling of chloride **3** with the mono-protected amine **90**, prepared from **89**, gave carbamate **91** which was deprotected under acidic conditions to give amine **92** which was reprotected as the trifluoroacetate **93** (Scheme 21). Oxidation of **93** with trifluoroperacetic acid gave 1,4-dioxide **94** which was deprotected under basic conditions and coupled to the imidazolide of acridine-4-carboxylic acid to give compound **95**.

Scheme 21



Reagents: (yield %)

a) BOC_2O, THF, 46%;

b) **3** + **90**, Et_3N, DME, 52% + 25% SM;

c) HCl, MeOH, 100%;

d) CF_3CO_2Et, H_2O, MeCN, 88%;

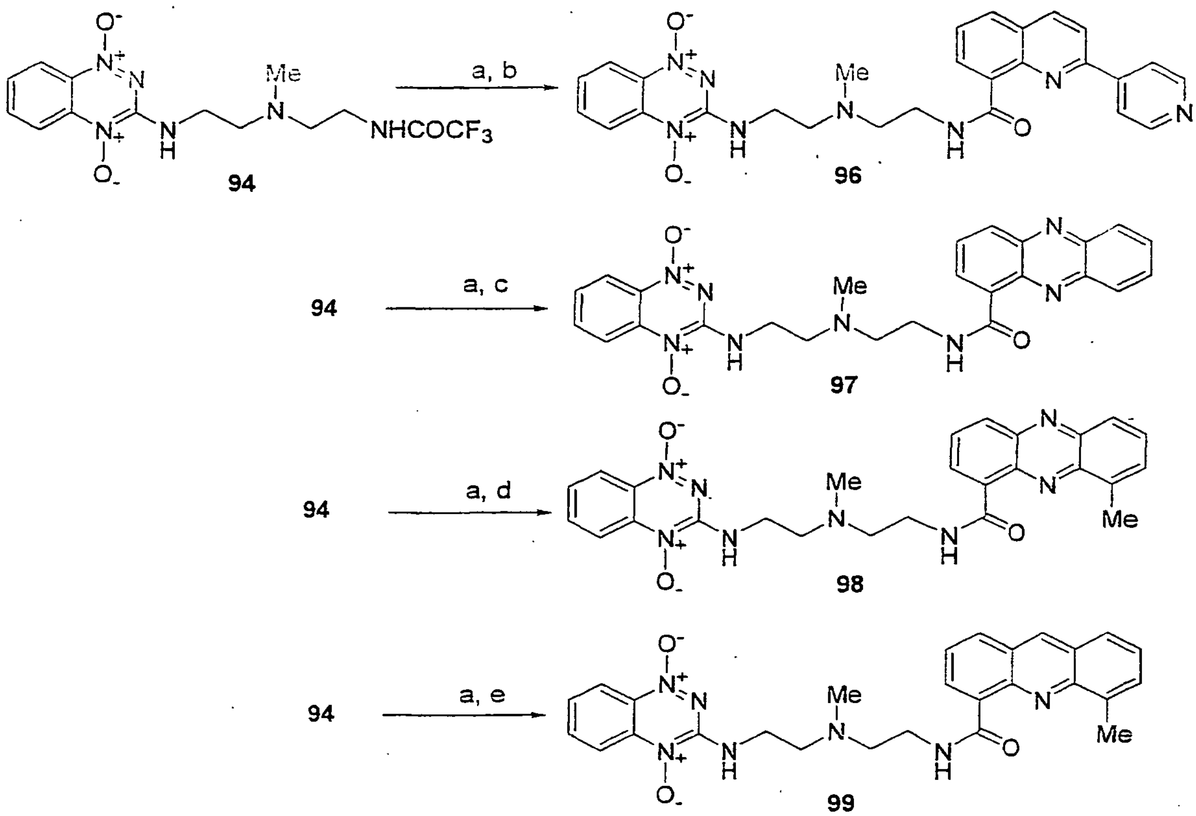
e) CF_3CO_3H, trifluoroacetic acid, DCM, 47% + 6% SM;

f) aqueous NH_3, MeOH;

g) acridine-4-carboxylic acid, CDI, DMF, 94%.

Similarly, deprotection of **94** and reaction with the imidazolides of 2-(4-pyridinyl)-8-quinolinecarboxylic acid, phenazine-1-carboxylic acid, 9-methylphenazine-1-carboxylic acid and 5-methylacridine-4-carboxylic acid gave compounds **96**, **97**, **98**, and **99** respectively (Scheme 22).

Scheme 22



Reagents: (yield %)

a) aqueous NH_3, MeOH;

b) 2-(4-pyridyl)quinoline-8-carboxylic acid, CDI, DMF, 97%;

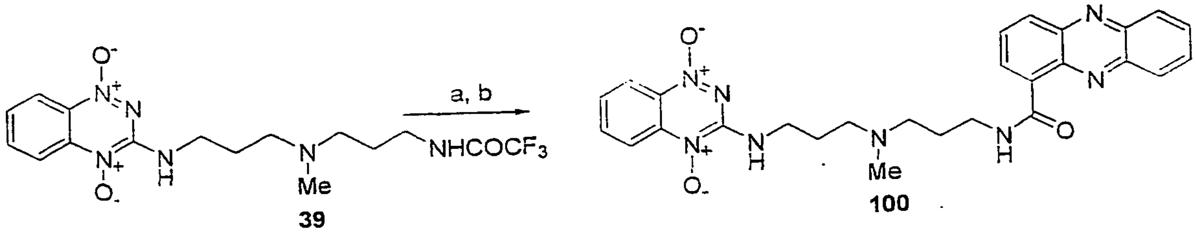
c) phenazine-1-carboxylic acid, CDI, DMF, 88%;

d) 9-methylphenazine-1-carboxylic acid, CDI, DMF, 80%;

e) 5-methylacridine-4-carboxylic acid, CDI, DMF, 100%.

Deprotection of trifluoroacetamide **39** under basic conditions and reaction with the imidazolide of phenazine-1-carboxylic acid gave compounds **100** (Scheme 23).

Scheme 23



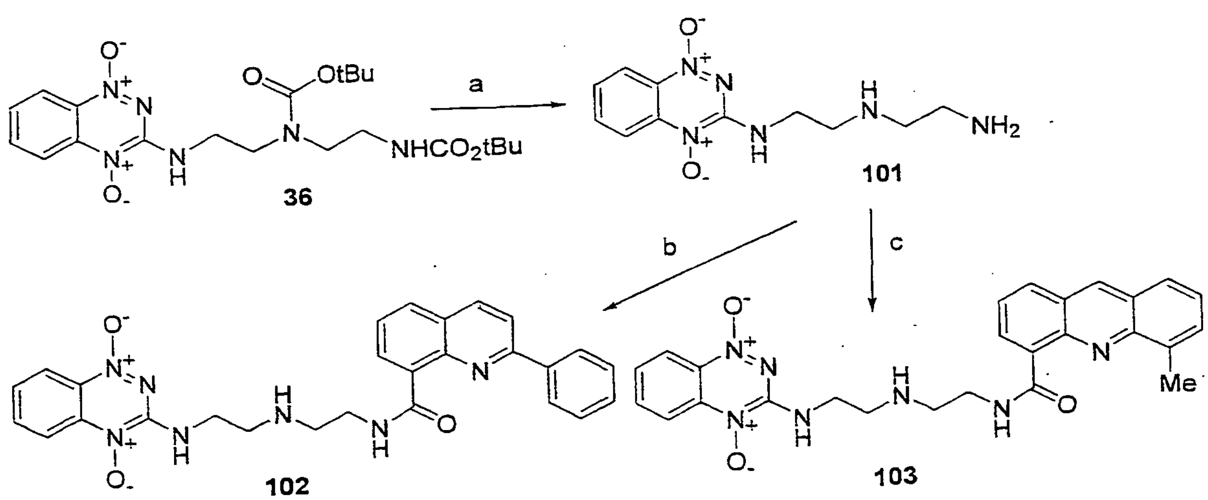
Reagents: (yield %)

a) aqueous NH_3, MeOH;

b) phenazine-1-carboxylic acid, CDI, DMF, 82%.

Deprotection of **36** and reaction with the imidazolides of 2-(4-pyridinyl)-8-quinolinecarboxylic acid and 5-methylacridine-4-carboxylic acid gave compounds **102** and **103** respectively (Scheme 24).

Scheme 24



Reagents: (yield %)

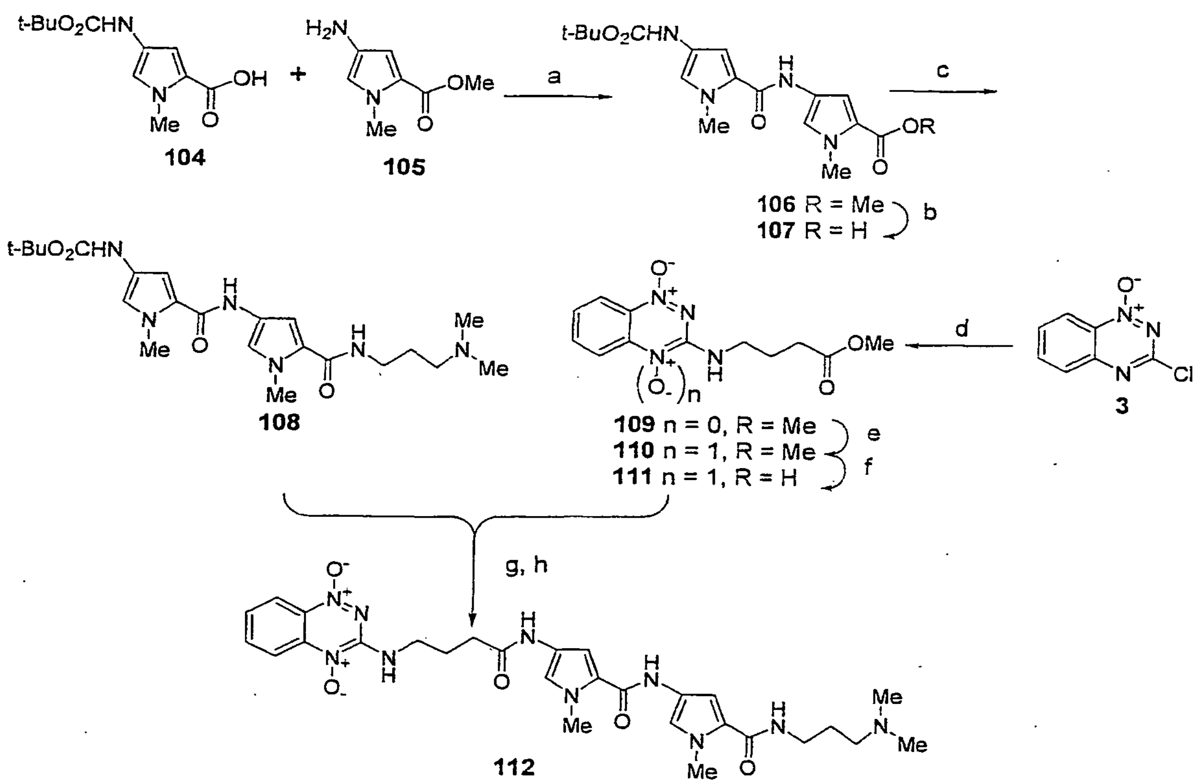
a) HCl/MeOH, 76%;

b) 2-(4-pyridyl)quinoline-8-carboxylic acid, CDI, DMF, 75%;

c) 5-methylacridine-4-carboxylic acid, CDI, DMF, 75%.

Coupling of acid **104** (Baird & Dervan, *J. Am. Chem. Soc*. **1996**, 118, 6141–6146) and amine **105** (Baird & Dervan, *J. Am. Chem. Soc*. **1996**, 118, 6141–6146) with EDCI and DMAP gave ester **106** (Scheme 25) which was hydrolysed under basic conditions to give acid **107**. Coupling of acid **107** and 3-dimethylaminopropylamine with EDCI and DMAP gave amide **108**. Reaction of chloride **3** with methyl 4-aminobutanoate gave ester **109** which was oxidised with trifluoroperacetic acid to give 1,4-dioxide **110** which was hydrolysed to acid **111**. Deprotection of carbamate **108** followed by coupling to acid **111** with EDCI and DMAP gave compound **112**.

Scheme 25



Reagents: (yield %)

a) **104** + **105**, EDCI, DMAP, DMF, DCM, 64%;

b) LiOH, THF, MeOH, 94%;

c) $NH_2(CH_2)_3NMe_2$, EDCI, DMAP, DMF, 76%;

d) $NH_2(CH_2)_3CO_2Me$, Et_3N, DME, 81%;

e) CF_3CO_3H, DCM, 33%;

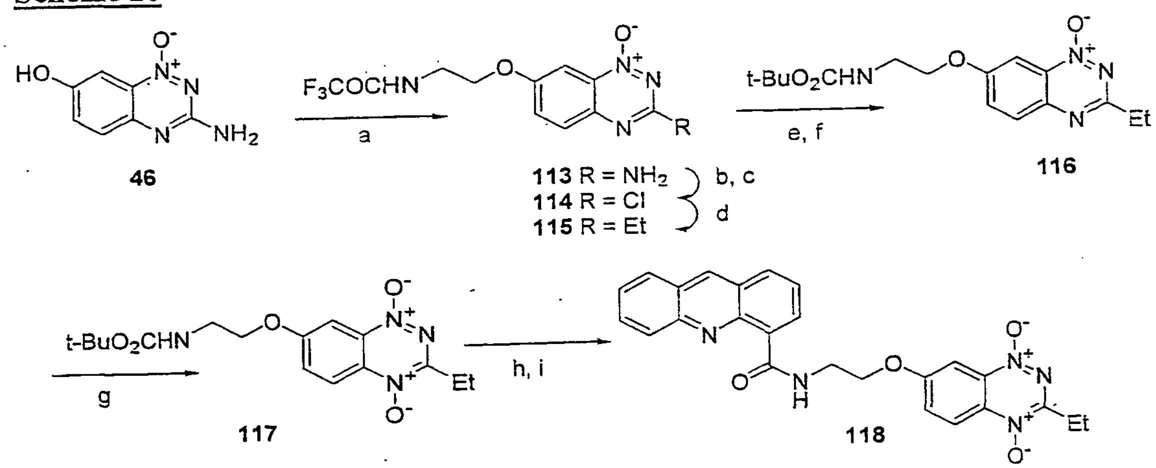
f) NaOH, MeOH, 81%;

g) HCl/MeOH;

h) **111**, EDCI, DMAP, DMF, DCM, 9%.

Reaction of the phenol **46** with the protected bromide gave compound **113** (Scheme 26) which underwent diazotization to the 3-hydroxy intermedaite and chlorination with $POCl_3$ to give chloride **114**. Stille coupling with tetraethyltin in the presence of a palladium catalyst gave the 3-ethyl compound **115**. Deprotection followed by reprotection with dibutyldicarbonate gave compound **116** which was oxidised with MCPBA to give dioxide **116**. Deprotection and coupling of the imidazolide of acridine-4-carboxylic acid is expected to afford compound **118**, a compound of Formula I'.

Scheme 26



Reagents: (yield %)

a) $CF_3CONHCH_2CH_2Br$, K_2CO_3, DMF, 66%;

b) $NaNO_2$, CF_3CO_2H, quant.;

c) $POCl_3$, quant.;

d) Et_4Sn, $Pd(PPh_3)_4$, DME, 79%;

e) aq. NH_3, MeOH, 80%;

f) BOC_2O, THF, 88%;

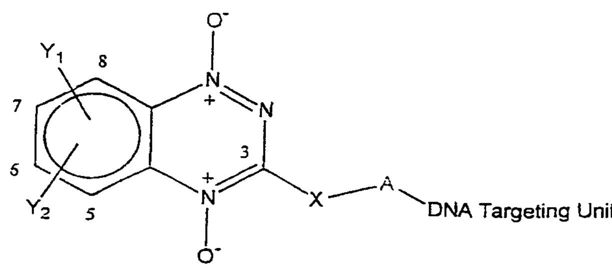
g) MCPBA, DCM, 76%;

h) aq. HCl, MeOH;

i) acridine-4-carboxylic acid, CDI, DMF.

Examples of the compounds of the invention

Table 1 gives details on examples of compounds within the scope of the invention, and preparable by the methods of the invention.



I

Table 1

Table 1. Examples of compounds

No.	#	Y_1	Y_2	X	A	DNA targeting unit	mp (°C)	Anal
11	3	H	H	NH	$(CH_2)_6$	9-NHacridine	118-119	C,H,N
12	3	H	H	NH	$(CH_2)_6$	4-NHCOacridine	196-198	C,H,N
13	3	H	H	NH	$(CH_2)_6$	4-NHquinoline	196-198	C,H,N
17	3	H	H	NH	$(CH_2)_3$	4-NHCOacridine	192	C,H,N
23	3	H	H	NH	$(CH_2)_2O(CH_2)_2$	4-NHCOacridine	98-100	C,H,N
24	3	H	H	NH	$(CH_2)_2O(CH_2)_2$	8-NHCOquinoline	168-170	C,H,N
25	3	H	H	NH	$(CH_2)_2O(CH_2)_2$	4-NHCObenz-imidazole-2-phenyl	203-207	C,H,N
26	3	H	H	NH	$(CH_2)_2O(CH_2)_2$	8-NHCOquinoline-2-(4-pyridyl)	128-130	C,H,N
30	3	H	H	NH	$(CH_2)_3NH(CH_2)_3$	4-NHCOacridine	gum	C,H,N
31	3	H	H	NH	$(CH_2)_3NH(CH_2)_3$	1-NHCOphenazine	163-169	C,H,N
32	3	H	H	NH	$(CH_2)_3NH(CH_2)_3$	1-NHCO-9-methyl-phenazine	183-186	HRMS
37	3	H	H	NH	$(CH_2)_2NH(CH_2)_2$	4-NHCOacridine	151-154	C,H,N
41	3	H	H	NH	$(CH_2)_3NMe(CH_2)_3$	4-NHCOacridine	169-171	HRMS
42	3	H	H	NH	$(CH_2)_3NMe(CH_2)_3$	8-NHCOquinoline	119-121	C,H,N
43	3	H	H	NH	$(CH_2)_3NMe(CH_2)_3$	8-NHCO-2-(4-pyridyl)quinoline	179-181	C,H,N
44	3	H	H	NH	$(CH_2)_3NMe(CH_2)_3$	4-NHCO-5-methylacridine	158-162	C,H,N
45	3	H	H	NH	$(CH_2)_3NMe(CH_2)_3$	1-NHCO-9-methylphenazine	138-142	C,H,N
55	3	†	H	NH	$(CH_2)_3NMe(CH_2)_3$	4-NHCOacridine	98-103	HRMS
62	3	H	H	CH_2	$(CH_2)_2NMe(CH_2)_3$	4-NHCOacridine	gum	HRMS
63	3	H	H	CH_2	$(CH_2)_2NMe(CH_2)_3$	1-NHCOphenazine	173	HRMS

65	3	H	H	NH	$(CH_2)_3NHCO(CH_2)_2$	4-NH-7-Clquinoline	202	HRMS
74	3	7-Me	H	NH	$(CH_2)_3NMe(CH_2)_3$	4-NHCOacridine	166-168	C,H,N
75	3	7-Me	H	NH	$(CH_2)_3NMe(CH_2)_3$	8-NHCO-2-(4-pyridyl)quinoline	178-180	C,H,N
76	3	7-Me	H	NH	$(CH_2)_3NMe(CH_2)_3$	1-NHCOphenazine	118-122	C,H,N
77	3	7-Me	H	NH	$(CH_2)_3NMe(CH_2)_3$	1-NHCO-9-methyl-phenazine	119-122	C,H,N
85	3	6-Me	H	NH	$(CH_2)_3NMe(CH_2)_3$	4-NHCOacridine	158-160	C,H,N
86	3	6-Me	H	NH	$(CH_2)_3NMe(CH_2)_3$	8-NHCO-2-(4-pyridyl)quinoline	178-180	C,H,N
87	3	6-Me	H	NH	$(CH_2)_3NMe(CH_2)_3$	1-NHCOphenazine	111-114	C,H,N
88	3	6-Me	H	NH	$(CH_2)_3NMe(CH_2)_3$	1-NHCO-9-methyl-phenazine	80-83	HRMS
95	3	H	H	NH	$(CH_2)_2NMe(CH_2)_2$	4-NHCOacridine	160-162	HRMS
96	3	H	H	NH	$(CH_2)_2NMe(CH_2)_2$	8-NHCO-2-(4-pyridyl)quinoline	130-135	C,H,N
97	3	H	H	NH	$(CH_2)_2NMe(CH_2)_2$	1-NHCOphenazine	163-165	C,H,N
98	3	H	H	NH	$(CH_2)_2NMe(CH_2)_2$	1-NHCO-9-methyl-phenazine	161-163	C,H,N
99	3	H	H	NH	$(CH_2)_2NMe(CH_2)_2$	4-NHCO-5-methylacridine	148-152	C,H,N
100	3	H	H	NH	$(CH_2)_3NMe(CH_2)_3$	1-NHCOphenazine	129-130	C,H,N
102	3	H	H	NH	$(CH_2)_2NH(CH_2)_2$	8-NHCO-2-(4-pyridyl)quinoline	160-165	C,H,N
103	3	H	H	NH	$(CH_2)_2NH(CH_2)_2$	4-NHCO-5-methylacridine	135-140	HRMS
112	3	H	H	NH	$(CH_2)_3CONH$	3-pyr-5-CONH-3-pyr-5-CONH$(CH_2)_3NMe_2$	140-145	C,H,N

Side chain position

†7-$MeOCH_2CH_2O$-

In the following examples representative of the invention and the detailed methods for preparing them:

Elemental analyses were carried out in the Microchemical Laboratory, University of Otago, Dunedin, NZ.

Melting points were determined on an Electrothermal 2300 Melting Point Apparatus. IR spectra were recorded on a Midac FT-IR as KBr discs, unless otherwise stated.

NMR spectra were obtained on a Bruker Avance-400 spectrometer at 400 MHz for ^1H and 100 MHz for ^{13}C spectra. Spectra were obtained in $CDCl_3$ unless otherwise specified, and are referenced to Me_4Si. Chemical shifts and coupling constants were recorded in units of ppm and Hz, respectively. Assignments were determined using COSY, HSQC, and HMBC two-dimensional experiments.

Mass spectra were determined on a VG-70SE mass spectrometer using an ionizing potential of 70 eV at a nominal resolution of 1000. High-resolution spectra were obtained at nominal resolutions of 3000, 5000, or 10000 as appropriate. All spectra were obtained as electron impact (EI) using PFK as the reference unless otherwise stated.

Solutions in organic solvents were dried with anhydrous Na_2SO_4. Solvents were evaporated under reduced pressure on a rotary evaporator.

Thin-layer chromatography was carried out on aluminium-backed silica gel plates (Merck 60 F_{254}) with visualization of components by UV light (254 nm) or exposure to I_2.

Column chromatography was carried out on silica gel, (Merck 230–400 mesh). All compounds designated for testing were analyzed at >99% purity by reverse phase HPLC using an Agilent 1100 liquid chromatograph, an Alltima C_{18} (5 μ) stainless steel column (150 mm × 3.2 mm i.d.) and an Agilent 1100 diode array detector. Chromatograms were run using various gradients of aqueous (0.045 M ammonium formate and formic acid at pH 3.5) and organic (80% MeCN/MilliQ water) phases. DCM refers to dichloromethane; DME refers to dimethoxyethane, DMF refers to dry dimethyl formamide; ether refers to diethyl ether; EtOAc refers to ethyl acetate; EtOH refers to ethanol; MeOH refers to methanol; pet. ether refers to petroleum ether, boiling range 40-60 °C; THF refers to tetrahydrofuran dried over sodium benzophenone ketyl. All solvents were freshly distilled.

Example A.

3-[(6-Aminohexyl)amino]-1,2,4-benzotriazine 1,4-dioxide (7).

3-Chloro-1,2,4-benzotriazine 1-oxide (3). 2-Nitroaniline (10 g, 72.4 mmol) and cyanamide (14.0 g, 330 mmol) were melted together and cHCl (20 mL) added cautiously. The mixture was heated at 100 °C until the foaming subsided. The mixture was made strongly alkaline with 30% w/v NaOH and heated at 100 °C for 10 min. The suspension was cooled to 25 °C and the yellow solid filtered, washed with water (20 mL) and dried. A small sample was recrystallized to give 3-amino-1,2,4-benzotriazine 1-oxide (**1**) mp (MeOH/EtOAc) 267-269 °C; lit. [Arndt, *Ber.* **1913**, 46, 3522–3529] mp (EtOH) 269 °C]. The remainder was dissolved in 2 M HCl (300 mL), cooled to 5 °C, and a solution of $NaNO_2$ (10 g, 0.145 mol) in water (100 mL) added dropwise. The resulting precipitate was filtered, dissolved in dilute NH_3, filtered, and acidified with cHCl. The precipitate was filtered, washed with water and dried to give 3-hydroxy-1,2,4-benzotriazine 1-oxide (**2**) (5.77 g, 49%) as a yellow powder, mp 209-212 °C; lit. [Arndt, *Ber.* **1913**, 46, 3522-3529] mp (H_2O) 219 °C]; ^{1}H NMR [$(CD_3)_2SO$] δ 8.14 (d, J = 8.4 Hz, 1 H, H-8), 7.77–7.81 (m, 1 H, H-6), 7.54 (d, J = 8.4 Hz, 1 H, H-5), 7.88–7.92 (m, 3 H, H-7, NH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 160.2, 148.7, 135.6, 129.8, 125.8, 124.6, 119.8. A mixture of the alcohol (**2**) (5.7 g, 34.9 mmol), *N,N*-dimethylaniline (11 mL, 87.3 mmol), and $POCl_3$ (23 mL, 244 mmol) was heated at reflux temperature for 1 h then poured on to ice. The resulting solid was filtered and recrystallized to give 3-chloro-1,2,4-benzotriazine 1-oxide (**3**) (3.77 g, 59%) as a pale yellow powder, mp 119–119.5 °C; lit. [Robbins *et al.*, *J. Chem. Soc.*, **1957**, 3186–3194] (MeOH) 117–118 °C]; ^{1}H NMR [$(CD_3)_2SO$] δ 8.38 (dd, J = 8.7, 1.0 Hz, 1 H, H-8), 8.16 (ddd, J = 8.3, 7.0, 1.3 Hz, 1 H, H-6), 8.06 (dd, J = 8.2, 1.0 Hz, 1 H, H-5), 7.90 (ddd, J = 8.7, 6.9, 1.3 Hz, 1 H, H-7); ^{13}C NMR [$(CD_3)_2SO$] δ 155.3, 146.9, 137.2, 133.9, 131.5, 128.0, 119.9.

6-*t*-Butyloxycarbamoylhexylamine (4). A solution of di-*t*-butyldicarbonate (18.6 g, 85.3 mmol) in dry DCM (100 mL) was added dropwise to a stirred solution of 6-aminohexanol (10.0 g, 85.3 mmol) in dry DCM (100 mL) at 20 °C and stirred for 16 h. The solution was washed with dilute aqueous Na_2CO_3 solution (100 mL), 0.1 M HCl (100 mL), water (100 mL), brine (50 mL), dried and the solvent evaporated. The

residue was dissolved in DCM (250 mL) and Et_3N (15.5 mL, 111 mmol) added. A solution of methanesulfonyl chloride (7.3 mL, 94 mmol) was added dropwise and the mixture stirred at 20 °C for 16 h. The solution was washed with saturated aqueous $KHCO_3$ (100 mL), water (2 × 100 mL), brine (50 mL), dried, and the solvent evaporated. The residue was dissolved in DMF (100 mL) and NaN_3 (5.55 g, 85.3 mmol) added. The mixture was stirred at 100 °C for 1 h, the solvent evaporated and the residue partitioned between EtOAc (200 mL) and water (200 mL). The organic fraction was washed with water (200 mL), brine (100 mL), dried and the solvent evaporated. The residue was purified by chromatography, eluting with 30% EtOAc/pet. ether, to give the 6-*t*-butyloxycarbamoylhexyl azide (17.5 g, 85%) as a colorless oil, ^{1}H NMR δ 4.53 (br s, 1 H, OCONH), 3.52 (t, J = 6.9 Hz, 2 H, CH_2N), 3.11 (dt, J = 6.5, 6.4 Hz, 2 H, CH_2N), 1.57–1.63 (m, 2 H, CH_2), 1.44–1.52 (m, 11 H, CH_2, $C(CH_3)_3$), 1.30–1.40 (m, 4 H, 2 × CH_2); ^{13}C NMR δ 156.0, 79.1, 51.3, 40.4, 29.9, 28.7, 28.4 (3), 26.4, 26.3. A mixture of azide (14.81 g, 61.1 mol) and Pd/C (0.5 g) in EtOAc/EtOH (200 mL) was stirred at 20 °C under hydrogen (60 psi) for 1 h. The mixture was filtered through celite, the cake washed with EtOAc (3 × 30 mL) and the solvent evaporated to give **4** (12.82 g, 97%) as a white solid, mp (EtOAc) 89–91 °C; ^{1}H NMR δ 4.65 (br s, 1 H, OCONH), 3.52 (br s, 2 H, NH_2), 2.69 (t, J = 6.9 Hz, 2 H, CH_2N), 1.88 (br s, 2 H, CH_2N), 1.44–1.50 [m, 13 H, 2 × CH_2, $C(CH_3)_3$], 1.29–1.35 (m, 4 H, 2 × CH_2); ^{13}C NMR δ 156.0, 78.9, 41.9, 40.4, 33.4, 29.9, 28.3 (3), 26.5, 26.4.

3-[(6-*t*-Butyloxycarbamoylhexyl)amino]-1,2,4-benzotriazine 1-oxide (5). A solution of amine **4** (12.8 g, 61.1 mmol) in DCM was added to a stirred solution of chloride **3** (3.70 g, 20.4 mmol) and Et_3N (5.7 mL, 40.8 mmol) in DCM (100 mL) and the solution stirred at 20 °C for 96 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (30-100%) of EtOAc/pet. ether, to give 1-oxide **5** (4.77 g, 65%) as a yellow powder, mp (EtOAc/pet. ether) 154–156 °C; ^{1}H NMR δ 8.26 (d, J = 8.6 Hz, 1 H, H-8), 7.70 (dd, J = 8.2, 7.2 Hz, 1 H, H-6), 7.59 (d, J = 8.5 Hz, 1 H, H-5), 7.27 (dd, J = 8.0, 7.5 Hz, 1 H, H-7), 5.34 (br s, 1 H, NH), 4.55 (br s, 1 H, OCONH), 3.51 (dd, J = 6.8, 6.6 Hz, 2 H, CH_2N), 3.10–3.13 (m, 2 H, CH_2N), 1.64–1.72 (m, 2 H, CH_2), 1.48–1.54 (m, 2 H, CH_2), 1.44 [s, 9 H, $C(CH_3)_3$], 1.38–1.43 (m, 4 H, 2 × CH_2); ^{13}C NMR δ 158.9, 155.5, 148.9, 135.5, 130.8, 126.4,

124.8, 120.4, 79.0, 41.2, 40.3, 30.0, 29.2, 28.4 (3), 26.4, 26.3. Anal. calcd for $C_{18}H_{27}N_5O_3$: C, 59.8; H, 7.5; N, 19.4; found:C, 59.6; H, 7.7; N, 19.2%.

3-[(6-*t*-Butyloxycarbamoylhexyl)amino]-1,2,4-benzotriazine 1,4-dioxide (6). A solution of MCPBA (1.48 g, 6.02 mmol) in DCM (20 mL) was added dropwise to a stirred solution of 1-oxide **5** (1.45 g, 4.01 mmol) in DCM (100 mL) at 20 °C and the solution stirred for 4 h. The solution was partitioned between DCM (200 mL) and saturated $KHCO_3$ solution (200 mL). The organic fraction was dried and the solvent evaporated. The residue was purified by chromatography on neutral alumina, eluting with 50% EtOAc/DCM then a gradient (0–10%) MeOH/$CHCl_3$, to give (i) starting material **5** (0.73 g, 50%), and (ii) 1,4-dioxide **6** (0.55 g, 37%) as a yellow powder, mp (EtOAc/DCM) 132–134 °C; IR (KBr) υ 3367, 3260, 1688, 1622, 1362, 1173 cm^{-1}; NMR $[(CD_3)_2SO]$ δ 8.30 (dd, $J = 6.3$, 6.1 Hz, 1 H, OCONH), 8.19 (d, $J = 8.5$ Hz, 1 H, H-8), 8.12 (d, $J = 8.5$ Hz, 1 H, H-5), 7.91–7.95 (m, 1 H, H-6), 7.53-7.57 (m, 1 H, H-7), 6.76 (br s, 1 H, NH), 3.32–3.39 (m, 2 H, CH_2N), 2.87–2.92 (m, 2 H, CH_2N), 1.56–1.61 (m, 2 H, CH_2), 1.32–1.40 [m, 13 H, 2 × CH_2, $C(CH_3)_3$], 1.25–1.31 (m, 2 H, CH_2); ^{13}C NMR $[(CD_3)_2SO]$ δ 155.5, 149.7, 138.1, 135.4, 129.8, 126.8, 121.1, 116.8, 77.2, 40.6, 39.8, 29.4, 28.6, 28.2 (3), 25.9, 25.8. Anal. calcd for $C_{18}H_{27}N_5O_4\cdot\frac{1}{4}H_2O$: C, 56.6; H, 7.3; N, 18.3; found: C, 56.8; H, 7.3; N, 16.8%.

***N*¹-(1,4-dioxido-1,2,4-benzotriazin-3-yl)-1,6-hexanediamine (7).** HCl gas was bubbled through a solution of carbamate **6** (204 mg, 0.54 mmol) in MeOH (20 mL) for 2 minutes and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between $CHCl_3$ (100 mL) and saturated $KHCO_3$ solution (100 mL). The aqueous fraction was further extracted with $CHCl_3$ (3 × 30 mL), the combined organic extracts dried, and the solvent evaporated to give amine **7** (127 mg, 85%) as a red powder, mp 120–122 °C, IR (KBR) υ 3250, 2926, 1616, 1599, 1410, 1356, 1078 cm^{-1}; ^1H NMR δ 8.34 (d, $J = 8.5$ Hz, 1 H, H-8'), 8.29 (d, $J = 8.6$ Hz, 1 H, H-5'), 7.87-7.90 (m, 1 H, H-6'), 7.48-7.52 (m, 1 H, H-7'), 7.13 (s, 1 H, NH), 3.60 (t, $J = 7.1$ Hz, 2 H, CH_2N), 2.70 (t, $J = 6.8$ Hz, 2 H, CH_2N), 1.70–1.76 (m, 2 H, CH_2), 1.35-1.50 (m, 6 H, 3 × CH_2); ^{13}C NMR $[(CD_3)_2SO]$ δ 149.7, 138.1, 135.4, 129.8, 126.7, 121.0, 116.8, 41.5, 40.6, 33.1, 28.7, 26.1, 26.0. Anal. calcd for $C_{13}H_{19}N_5O_2$: C, 56.3; H, 6.9; N, 25.3; found: C, 56.3; H, 6.8; N, 22.2%. The compound was dissolved

in MeOH, treated with HCl gas, and the solvent evaporated. The residue was crystallized to give the dihydrochloride of **7** as a red powder, mp (MeOH/EtOAc) 150 °C (dec.).

N^1-(1-Oxido-1,2,4-benzotriazin-3-yl)-1,6-hexanediamine (8). HCl gas was bubbled through a solution of carbamate **5** (1.0 g, 2.77 mmol) in MeOH (80 mL) for 2 minutes and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between $CHCl_3$ (100 mL) and Na_2CO_3 solution (100 mL). The aqueous fraction was further extracted with $CHCl_3$ (3 × 30 mL), the combined organic extracts dried, and the solvent evaporated to give amine **8** (0.63 g, 87%) as a red powder, mp 132–134 °C, ^{1}H NMR δ 8.25 (dd, J = 8.6, 1.0 Hz, 1 H, H-8'), 7.66–7.71 (m, 1 H, H-6'), 7.59 (d, J = 8.4 Hz, 1 H, H-5'), 7.26-7.30 (m, 1 H, H-7'), 5.48 (br s, 1 H, NH), 3.52 (dd, J = 6.9, 6.3 Hz, 2 H, H-1), 2.69 (dd, J = 6.8, 6.6 Hz, 2 H, H-6), 1.64–1.71 (m, 2 H, H-2), 1.35–1.48 (m, 8 H, H-3, H-4, H-5, NH_2); ^{13}C NMR δ 159.0, 148.9, 135.5, 130.8, 126.4, 124.7, 120.4, 42.0, 41.3, 33.6, 29.3, 26.6, 26.5. Anal. calcd for $C_{13}H_{19}N_5O$: C, 59.7; H, 7.3; N, 26.8; found: C, 59.5; H, 7.5; N, 26.5%.

Oxidation of N^1-(1-oxido-1,2,4-benzotriazin-3-yl)-1,6-hexanediamine (8). Trifluoroacetic anhydride (11.9 mL) was added to a stirred solution of amine **8** (1.1 g, 4.2 mmol) in DCM (100 mL) and the solution stirred at 20 C for 30 min. The solution was cooled to 5 °C and 35% H_2O_2 (11.9 mL, ca 105 mmol) added dropwise and the mixture stirred vigorously for 16 h. The mixture was concentrated to 30 mL (CAUTION) and partitioned between DCM (100 mL) and sat. aqueous $KHCO_3$ solution (50 mL). The aqueous fraction was extracted with DCM (3 × 50 mL), the combined organic fraction dried and the solvent evaporated (CAUTION). The residue was purified by chromatography, eluting with a gradient (0–10%) MeOH/(40–0%) EtOAc/DCM, to give (i) 2,2,2-trifluoro-*N*-{6-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]hexyl}acetamide (**9**) (0.77 g, 51%) as a yellow solid, mp (EtOAc/DCM) 188–189 °C; IR (KBr) υ 3306, 1699, 1588, 1570, 1176 cm^{-1}; ^{1}H NMR δ 8.27 (dd, J = 8.7, 1.3 Hz, 1 H, H-8'), 7.70 (ddd, J = 8.5, 6.9, 1.3 Hz, 1 H, H-6'), 7.59 (d, J = 8.5 Hz, 1 H, H-5'), 7.29 (ddd, J = 8.7, 6.9, 1.3 Hz, 1 H, H-7'), 6.33 (br s, 1 H, NH), 5.22 (s, 1 H, CONH), 3.51 (q, J = 6.9 Hz, 2 H, H-1), 3.38 (q, J = 6.8 Hz, 2 H, H-6), 1.66–1.73 (m, 2 H, H-5), 1.59–1.65 (m, 2 H, H-2), 1.40–1.47 (m, 4 H, H-3, H-4); ^{13}C NMR δ

158.7, 156.8 (q, J = 37 Hz), 148.6, 135.0, 130.2, 126.0, 124.1, 119.8, 115.7 (q, J = 288 Hz), 40.6, 39.2, 28.6, 28.2, 25.9, 25.8. Anal. calcd for $C_{15}H_{18}F_3N_5O_2$: C, 50.4; H, 5.1; N, 19.6; found: C, 50.7; H, 4.9; N, 19.6%, and:

(ii) *N*-{6-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]hexyl}-2,2,2-trifluoroacetamide (**10**) (346 mg, 22%) as a red solid, mp (MeOH/DCM) 163–165 °C; IR (KBr) υ 3437, 3266, 1699, 1634, 1178 cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 9.42 (s, 1 H, NH), 8.31 (t, J = 6.0 Hz, 1 H, CONH), 8.20 (d, J = 8.7 Hz, 1 H, H-8'), 8.12 (d, J = 8.6 Hz, 1 H, H-5'), 7.91–7.95 (m, 1 H, H-6'), 7.53–7.57 (m, 1 H, H-7'), 3.40 (q, J = 6.7 Hz, 2 H, H-1), 3.18 (q, J = 6.6 Hz, 2 H, H-6), 1.58–1.64 (m, 2 H, H-2), 1.46–1.53 (m, 2 H, H-5), 1.28–1.38 (m, 4 H, H-3, H-4); ^{13}C NMR [$(CD_3)_2SO$] δ 156.0 (q, J = 36 Hz), 149.7, 138.1, 135.4, 129.8, 126.7, 121.1, 116.8, 115.9 (q, J = 288 Hz), 40.5, 39.0, 28.5, 28.1, 25.8, 25.7. Anal. calcd for $C_{15}H_{18}F_3N_5O_3$: C, 48.3; H, 4.9; N, 18.8; found: C, 48.5; H, 4.7; N, 18.0%.

Oxidation of 2,2,2-trifluoro-*N*-{6-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]hexyl}acetamide (9). Trifluoroacetic anhydride (4.0 mL, 28.6 mmol) was added dropwise to a stirred suspension of 35% H_2O_2 (2.2 mL, ca. 23 mmol) in DCM (20 mL) at 5 °C and the mixture was stirred for 15 min. The mixture was dried and added to a stirred solution of 1-oxide **9** (409 mg, 1.14 mmol) in DCM (50 mL) and the solution stirred at 20 °C for 48 h. The solution was partitioned between sat. aqueous $KHCO_3$ (50 mL) and $CHCl_3$ (50 mL). The aqueous fraction was extracted with $CHCl_3$ (3 × 40 mL), the combined organic fraction dried, and the solvent evaporated (CAUTION). The residue was purified by chromatography, eluting with a gradient (0–10%) MeOH/(40–0%) EtOAc/DCM, to give (i) starting material **9** (250 mg, 61%); and (ii) 1,4-dioxide **10** (124 mg, 29%), spectroscopically identical to a sample obtained above.

***N*¹-(1,4-Dioxido-1,2,4-benzotriazin-3-yl)-1,6-hexanediamine** (7). 1 M NaOH solution (2.8 mL, 2.8 mmol) was added to a stirred solution of trifluoroacetamide **10** (209 mg, 0.56 mmol) in MeOH (20 mL) and the mixture stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between sat. aqueous $KHCO_3$ (70 mL) and $CHCl_3$ (70 mL). The aqueous fraction was extracted with $CHCl_3$ (3 × 30

mL), the combined organic fraction dried, and the solvent evaporated to give amine 7 (129 mg, 83%), spectroscopically identical with the sample obtained above.

Example B.

***N*[1]-(9-Acridinyl)-*N*[6]-(1,4-dioxido-1,2,4-benzotriazin-3-yl)-1,6-hexanediamine (11).** A solution of amine 7 (64 mg, 0.23 mmol) and 9-methoxyacridine (53 mg, 0.25 mmol) in MeOH (10 mL) was stirred at reflux temperature for 10 h. The solvent was evaporated and the residue purified by chromatography on neutral alumina, eluting with a gradient (0–5%) of MeOH/$CHCl_3$, to give compound **11** (63 mg, 60%) as a red solid, IR (KBr) υ 3293, 1593, 1414, 1362 cm^{-1}; ^{1}H NMR δ 8.30 (d, J = 8.5 Hz, 1 H, H-8"), 8.29 (d, J = 8.5 Hz, 1 H, H-5"), 8.11 (d, J = 8.6 Hz, 2 H, H-1', H-8'), 8.04 (d, J = 8.6 Hz, 2 H, H-4', H-5'), 7.84 (ddd, J = 8.5, 7.2, 1.2 Hz, 1 H, H-6"), 7.59–7.64 (m, 2 H, H-3', H-6'), 7.57 (ddd, J = 8.5, 7.2, 1.2 Hz, 1 H, H-7"), 7.31–7.35 (m, 2 H, H-2', H-7'), 7.15 (br s, 1 H, NH), 3.84 (dd, J = 7.2, 7.1 Hz, 2 H, CH_2N), 3.57 (dt, J = 6.7, 6.5 Hz, 2 H, CH_2N), 1.78–1.85 (m, 2 H, CH_2), 1.67–1.74 (m, 2 H, CH_2), 1.43–1.53 (m, 4 H, 2 × CH_2), NH not observed; ^{13}C NMR δ 151.9 (2), 149.8, 148.0, 138.1, 135.8, 130.3, 130.2 (2), 128.1 (2), 127.1, 123.0 (2), 122.9 (2), 121.6, 117.2, 116.1 (2), 50.4, 41.2, 31.4, 29.2, 26.4, 26.3; MS (FAB$^+$) m/z 455 (MH^+, 20%), 439 (10); HRMS (FAB$^+$) calcd for $C_{26}H_{27}N_6O_2$ (MH+) m/z 455.2196, found 455.2182. The compound was dissolved in MeOH and treated with HCl gas and the solvent evaporated. The residue was crystallized from MeOH/EtOAc to give the hydrochloride of **11**, mp (MeOH/EtOAc) 118–119 °C. Anal. calcd for $C_{26}H_{26}N_6O_2\cdot 2HCl\cdot \frac{1}{2}H_2O$: C, 58.2; H, 5.5; N, 15.7; found: C, 57.8; H, 5.5; N, 15.3%.

Example C.

***N*-{6-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]hexyl}-4-acridinecarboxamide (12).** A solution of the amine 7 (447 mg, 1.6 mmol) in THF (20 mL) and DMF (10 mL) was added dropwise to a stirred solution of acridine-4-carboxylic acid imidazolide (440 mg, 1.61 mmol) in THF (20 mL) at 5 °C and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give compound **12** (708 mg, 91%) as a red solid, mp (EtOAc) 196–198 °C; ^{1}H NMR δ 11.88 (s, 1 H, NH), 8.99 (dd, J = 7.1, 1.5 Hz, 1 H, H-3), 8.90 (s, 1 H, H-9), 8.30 (d, J = 8.4 Hz, 1 H,

H-8'), 8.28 (d, J = 8.7 Hz, 1 H, H-5'), 8.17 (d, J = 9.1 Hz, 1 H, H-5), 8.14 (dd, J = 8.4, 1.5 Hz, 1 H, H-1), 8.04 (d, J = 8.1 Hz, 1 H, H-8), 7.84–7.91 (m, 2 H, H-6, H-6'), 7.66 (dd, J = 8.3, 7.2 Hz, 1 H, H-2), 7.59 (ddd, J = 7.9, 7.0, 0.9 Hz, 1 H, H-7), 7.59 (ddd, J = 8.4, 7.2, 1.2 Hz, 1 H, H-7'), 7.11 (br dd, J = 5.7, 5.5 Hz, 1 H, CONH), 3.71 (dd, J = 6.9, 5.6 Hz, 2 H, CH_2N), 3.63 (dd, J = 6.9, 6.7 Hz, 2 H, CH_2N), 1.83–1.89 (m, 2 H, CH_2), 1.74–1.81 (m, 2 H, CH_2), 1.55–1.68 (m, 4 H, 2 × CH_2); ^{13}C NMR δ 164.6, 149.7, 147.0, 145.5, 145.0, 138.7, 138.1, 135.4, 134.5, 132.8, 132.0, 129.8, 128.5, 128.3, 126.8, 126.5, 126.4, 125.6, 125.3, 121.1, 116.8, 40.6, 39.0, 29.0, 29.6, 26.5, 26.0. Anal. calcd for $C_{27}H_{26}N_6O_0{\cdot}H_2O$: C, 64.8; H, 5.6; N, 16.8; found: C, 65.0; H, 5.5; N, 17.1%.

Example D.

***N*-{6-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]hexyl}-4-quinolinecarboxamide (13).** A solution of 4-quinolinecarboxylic acid (308 mg, 1.78 mmol) and CDI (346 mg, 2.13 mmol) in DMF (20 mL) were stirred at 50 °C for 1 h. The solvent was evaporated and the residue recrystallised from DCM/pet. ether to give 4-(1*H*-imidazol-1-ylcarbonyl)quinoline which was used directly without characterisation. A solution of the amine **7** (494 mg, 1.78 mmol) in DMF (10 mL) was added dropwise to a stirred solution of imidazolide in THF (20 mL) at 5 °C and the solution was stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give compound **13** (619 mg, 80%) as a red powder, mp (MeOH/DCM) 196–198 °C; ^{1}H NMR $[(CD_3)_2SO]$ δ 8.96 (d, J = 4.3 Hz, 1 H, H-2), 8.75 (t, J = 5.5 Hz, 1 H, CONH), 8.32 (t, J = 6.1 Hz, 1 H, NH), 8.20 (d, J = 8.6 Hz, 1 H, H-8"), 8.12 (d, J = 8.6 Hz, 1 H, H-5"), 8.11 (d, J = 8.7 Hz, 1 H, H-5), 8.06 (d, J = 8.4 Hz, 1 H, H-8), 7.92 (ddd, J = 8.4, 7.1, 1.3 Hz, 1 H, H-6"), 7.80 (ddd, J = 8.4, 7.1, 1.0 Hz, 1 H, H-7), 7.66 (ddd, J = 8.5, 7.0, 1.0 Hz, 1 H, H-6), 7.55 (ddd, J = 8.5, 7.1, 1.3 Hz, 1 H, H-7"), 7.52 (d, J = 4.4 Hz, 1 H, H-3), 3.39-3.43 (m, 2 H, H-1'), 3.3–3.35 (m, 2 H, H-6'), 1.65–1.70 (m, 2 H, H-2'), 1.56–1.73 (m, 2 H, H-5'), 1.38–1.45 (m, 4 H, H-3', H-4'); ^{13}C NMR $[(CD_3)_2SO]$ δ 166.4, 150.2, 149.7, 147.8, 142.4, 138.1, 135.4, 129.8, 129.6, 129.2, 127.1, 126.7, 125.3, 124.1, 121.0, 118.8, 116.7, 40.6, 38.9, 28.8, 28.6, 26.1, 25.9. Anal. calcd for $C_{23}H_{24}N_6O_3$: C, 63.9; H, 5.6; N, 19.4; found: C, 63.9; H, 5.4; N, 19.5%.

Example E.

***N*-{3-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}-4-acridinecarboxamide (17).**

***tert*-Butyl 3-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]propylcarbamate (14).** A solution of chloride **3** (4.0 g, 22.0 mmol), *tert*-butyl 3-aminopropylcarbamate (5.76 g, 33.0 mmol) and Et_3N (4.6 mL, 33.0 mmol) in DCM (150 mL) was stirred at 20 °C for 5 d. The solvent was evaporated, and the residue purified by chromatography, eluting with 20% EtOAc/DCM, to give 1-oxide **14** (5.21 g, 74%) as a yellow powder, mp (EtOAc/DCM) 145–147 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.13 (dd, J = 8.6, 1.1 Hz, 1 H, H-8'), 7.84 (s, 1 H, NH), 7.78 (ddd, J = 8.4, 7.1, 1.1 Hz, 1 H, H-6'), 7.56 (d, J = 8.4 Hz, 1 H, H-5'), 7.32 (ddd, J = 8.6, 7.1, 1.1 Hz, 1 H, H-7'), 6.83 (t, J = 5.3 Hz, 1 H, $NHCO_2$), 3.32–3.36 (m, 2 H, H-1), 2.99–3.04 (m, 2 H, H-3), 1.66–1.73 (m, 2 H, H-2), 1.37 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR [$(CD_3)_2SO$] δ 158.9, 155.6, 148.2, 135.7, 130.0, 125.9, 124.4, 119.9, 77.4, 38.2, 37.5, 28.9, 28.2 (3). Anal. calcd for $C_{15}H_{21}N_5O_3$: C, 56.4; H, 6.6; N, 21.9; found: C, 56.4; H, 6.6; N, 22.1%.

***tert*-Butyl 3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propylcarbamate (15).** A solution of MCPBA (6.74g, 27.3 mmol) in DCM (80 mL) was added dropwise to a stirred solution of 1-oxide **14** (5.82 g, 18.2 mmol) in DCM (300 mL) and $NaHCO_3$ (3.1 g, 36.5 mmol). The mixture was stirred at 20 °C for 1 h, partitioned between DCM (400 mL) and sat. aqueous $KHCO_3$ solution (100 mL). The organic fraction was dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–10%) of MeOH/40%EtOAc/DCM, to give (i) starting material **14** (2.63 g, 45%) and (ii) 1,4-dioxide **15** (1.47 g, 24%) as a red solid, mp (EtOAc/MeOH) 134–136 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.30 (t, J = 6.2 Hz, 1 H, NH), 8.20 (d, J = 8.5 Hz, 1 H, H-8'), 8.13 (d, J = 8.5 Hz, 1 H, H-5'), 7.93 (ddd, J = 8.5, 7.1, 1.3 Hz, 1 H, H-6'), 7.57 (ddd, J = 8.5, 7.1, 1.3 Hz, 1 H, H-7'), 6.86 (t, J = 5.6 Hz, 1 H, $NHCO_2$), 3.38–3.42 (m, 2 H, H-1), 2.98–3.02 (m, 2 H, H-3), 1.68–1.74 (m, 2 H, H-2), 1.37 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR [$(CD_3)_2SO$] δ 155.6, 149.7, 138.1, 135.4, 129.8, 126.8, 121.0, 116.8, 77.4, 38.2, 37.1, 28.9, 28.1 (3). Anal. calcd for $C_{15}H_{21}N_5O_4 \cdot \frac{1}{4}EtOAc$: C, 53.8; H, 6.5; N, 19.6; found: C, 53.5; H, 6.5; N, 19.5%.

N^1-(1,4-Dioxido-1,2,4-benzotriazin-3-yl)-1,3-propanediamine (16). HCl saturated MeOH (20 mL) was added to a solution of carbamate **15** (1.47 mg, 4.38 mmol) in MeOH (30 mL) and the solution stirred at 20 °C for 16 h. The solution was evaporated and the residue dissolved in water (20 mL) the solution neutralized with $KHCO_3$ and extracted with $CHCl_3$ (5 × 50 mL). The combined organic fraction was dried and the solvent evaporated to give compound **16** (0.82 g, 80%) as a red solid, mp (MeOH) 121–123 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.24 (d, J = 8.4 Hz, 1 H, H-8'), 8.13 (d, J = 8.6 Hz, 1 H, H-5'), 7.99 (ddd, J = 8.6, 7.1, 1.0 Hz, 1 H, H-6'), 7.61 (ddd, J = 8.4, 7.1, 1.0 Hz, 1 H, H-7'), 4.01 (br s, 3 H, NH, NH_2), 3.48 (t, J = 6.7 Hz, 2 H, H-1), 2.66 (t, J = 7.0 Hz, 2 H, H-3), 1.73–1.77 (m, 2 H, H-2); MS (FAB$^+$) *m/z* 236 (MH$^+$, 6%), 220 (10), 204 (5); HRMS calcd for $C_{10}H_{14}N_5O_2$ (MH$^+$) *m/z* 236.1148, found 236.1139.

***N*-{3-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}-4-acridinecarboxamide (17)**. A solution of amine **16** (128 mg, 0.54 mmol) in DCM (5 mL) was added dropwise to a stirred solution of 4-(1*H*-imidazol-1-ylcarbonyl)acridine (156 mg, 0.57 mmol) in DCM (10 mL) at 5 °C and the solution was stirred at 20 °C for 6 d. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give compound **17** (102 mg, 80%) as a red gum, ^{1}H NMR [$(CD_3)_2SO$] δ 11.39 (t, J = 5.5 Hz, 1 H, CONH), 9.31 (s, 1 H, H-9), 8.71 (dd, J = 7.1, 1.4 Hz, 1 H, H-3), 8.48 (br s, 1 H, NH), 8.38 (dd, J = 8.4, 1.4 Hz, 1 H, H-1), 8.33 (d, J = 9.2 Hz, 1 H, H-5), 8.22 (d, J = 8.5 Hz, 1 H, H-8), 8.13 (d, J = 8.4 Hz, 1 H, H-8'), 8.06 (d, J = 8.7 Hz, 1 H, H-5'), 7.87–7.95 (m, 2 H, H-6, H-6'), 7.76 (dd, J = 8.4, 7.1 Hz, 1 H, H-2), 7.68 (dd, J = 8.5, 7.2 Hz, 1 H, H-7), 7.54 (ddd, J = 8.5, 7.1, 1.3 Hz, 1 H, H-7'), 3.64–3.70 (m, 4 H, 2 CH_2N), 2.05–2.10 (m, 2 H, CH_2); ^{13}C NMR (CD_3OD) δ 168.9, 152.2, 151.5 (2), 141.0, 140.5, 140.1 (2), 138.8, 137.9, 135.7, 133.7, 131.5, 130.1, 128.9, 128.5, 128.1, 127.0, 123.0, 121.9, 121.6, 40.6, 38.1, 29.6. An analytical sample was recrystallized as the dihydrochloride salt, mp (MeOH/EtOAc) 192 °C. Anal. calcd for $C_{24}H_{20}N_6O_3 \cdot 2HCl \cdot ½H_2O$: C, 55.2; H, 4.4; N, 16.1; found: C, 55.3; H, 4.5; N, 16.1%.

Example F.

N-(2-{2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethoxy}ethyl)-4-acridinecarboxamide (23).

3-{[2-(2-Hydroxyethoxy)ethyl]amino}-1,2,4-benzotriazine 1-oxide (18). A solution of chloride 3 (3.0 g, 16.52 mmol) in DCM (50 mL) was added to a stirred solution of 2-(aminoethoxy)ethanol (2.49 mL, 24.8 mmol) and Et_3N (3.45 mL, 24.8 mmol) in DCM (80 mL) and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with 40% EtOAc/DCM, to give 1-oxide **18** (2.62 g, 63%) as a yellow powder, mp (DCM/EtOAc) 131–131.5 °C; ^{1}H NMR δ 8.25 (dd, J = 8.7, 1.2 Hz, 1 H, H-8), 7.68 (ddd, J = 8.4, 7.2, 1.5 Hz, 1 H, H-6), 7.57 (d, J = 8.4 Hz, 1 H, H-5), 7.28 (ddd, J = 8.7, 7.2, 1.3 Hz, 1 H, H-7), 6.02 (br s, 1 H, NH), 3.74–3.80 (m, 6 H, 3 × CH_2O), 3.64–3.67 (m, 2 H, CH_2N), 2.71 (t, J = 5.9 Hz, 1 H, OH); ^{13}C NMR δ 158.9, 149.7, 135.5, 130.9, 126.4, 124.9, 120.4, 72.4, 69.5, 61.7, 41.9. Anal. calcd for $C_{11}H_{14}N_4O_3$: C, 52.8; H, 5.6; N, 22.4; found: C, 52.9; H, 5.7; N, 22.6%.

3-{[2-(2-Azidoethoxy)ethyl]amino}-1,2,4-benzotriazine 1-oxide (19). Methanesulfonyl chloride (0.82 mL, 10.6 mmol) was added dropwise to a stirred solution of alcohol **18** (2.41 g, 9.63 mmol) and Et_3N (1.74 mL, 12.5 mmol) in DCM (100 mL) at 5 °C and the solution stirred at 20 °C for 1 h. The solution was diluted with DCM (100 mL) and washed with water (3 × 50 mL), brine (50 mL), dried and the solvent evaporated. The residue was dissolved in DMF (50 mL) and NaN_3 (0.69 g, 10.6 mmol) added. The mixture was heated at 100 °C for 2 h, cooled to 30 °C and the solvent evaporated. The residue was partitioned between EtOAc (100 mL) and water (100 mL). The organic fraction was washed with brine (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 50% EtOAc/pet. ether, to give azide **19** (2.35 g, 89%) as yellow crystals, mp (EtOAc/pet. ether) 102–104 °C; ^{1}H NMR δ 8.27 (dd, J = 8.7, 1.4 Hz, 1 H, H-8), 7.70 (ddd, J = 8.6, 7.1, 1.5 Hz, 1 H, H-6), 7.59 (d, J = 8.6 Hz, 1 H, H-5), 7.29 (ddd, J = 8.6, 7.1, 1.4 Hz, 1 H, H-7), 5.70 (br s, 1 H, NH), 3.71–3.78 (m, 4 H, 2 × CH_2O), 3.69 (dd, J = 5.3, 4.8 Hz, 2 H, CH_2N_3), 3.41 (dd, J = 5.1, 4.9 Hz, 2 H, CH_2N); ^{13}C NMR δ 158.9, 148.7, 135.5, 131.1, 126.5, 125.0, 120.4, 70.0, 69.6, 50.7, 41.1. Anal. calcd for $C_{11}H_{13}N_7O_2$; C, 48.0; H, 4.8; N, 35.6; found: C, 48.3; H, 4.6; N, 35.7%.

3-{[2-(2-*tert*-Butyloxycarbamoylethoxy)ethyl]amino}-1,2,4-benzotriazine 1-oxide (20). Propane-1,3-dithiol (5.7 mL, 57.0 mmol) was added dropwise to a stirred solution of azide **19** (1.57 g, 5.70 mmol) and Et_3N (7.95 mL, 57 mmol) in MeOH (100 mL) under N_2 and the solution heated at reflux temperature for 8 h. The solution was cooled to 30 °C and partitioned between 1 M HCl (100 mL) and Et_2O (100 mL). The aqueous fraction was adjusted to pH 12 with 7 M NaOH solution and extracted with DCM (3 × 50 mL). The organic fraction was dried and the solvent evaporated. The residue was dissolved in THF (100 mL) and a solution of di-*tert*-butyldicarbonate (1.87 g, 8.55 mmol) in THF (50 mL) added dropwise. The solution was stirred at 20 °C for 16 h, the solvent evaporated and the residue purified by chromatography, eluting with 40% EtOAc/pet. ether, to give carbamate **20** (1.85 g, 93%) as a yellow solid, mp (EtOAc/pet. ether) 134–137 °C; ^{1}H NMR δ 8.26 (dd, J = 8.4, 0.9 Hz, 1 H, H-8), 7.71 (ddd, J = 8.3, 7.1, 1.4 Hz, 1 H, H-6), 7.59 (d, J = 8.3 Hz, 1 H, H-5), 7.29 (ddd, J = 8.4, 7.1, 1.3 Hz, 1 H, H-7), 5.74 (br s, 1 H, NH), 4.93 (br s, 1 H, NH), 3.67–3.73 (m, 4 H, 2 × CH_2O), 3.56 (t, J = 5.2 Hz, 2 H, CH_2N), 3.29–3.36 (m, 2 H, CH_2N), 1.45 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR δ 159.9, 155.9, 148.7, 135.5, 131.0, 126.5, 125.0, 120.4, 79.4, 70.2, 69.2, 41.1, 40.4, 28.4 (3). Anal. calcd for $C_{16}H_{23}N_5O_4$: C, 55.0; H, 6.6; N, 20.1; found: C, 55.3; H, 6.8; N, 20.1%.

3-{[2-(2-*tert*-Butyloxycarbamoylethoxy)ethyl]amino}-1,2,4-benzotriazine 1,4-dioxide (21). A solution of MCPBA (1.57 g, 6.35 mmol) in DCM (50 mL) was added dropwise to a stirred solution of carbamate **20** (1.85 g, 5.29 mmol) in DCM (100 mL) and $NaHCO_3$ (0.89 g, 10.6 mmol) and the mixture was stirred at 20 °C for 6 h. The suspension was filtered through celite, the solvent evaporated and the residue purified by chromatography, eluting with a gradient of (0–5%) MeOH/(40–0%) EtOAc/DCM, to give (i) starting material **20** (926 mg, 50%), spectroscopically identical with an authentic sample, and (ii) 1,4-dioxide **21** (702 mg, 40%) as a red solid, mp (EtOAc) 139–140 °C; ^{1}H NMR δ 8.33 (d, J = 8.7 Hz, 1 H, H-8), 8.30 (d, J = 8.7 Hz, 1 H, H-5), 7.88 (ddd, J = 8.7, 7.2, 1.2 Hz, 1 H, H-6), 7.43–7.50 (m, 2 H, H-7, NH), 5.06 (br s, 1 H, NH), 3.78–3.83 (m, 2 H, CH_2O), 3.69 (dd, J = 5.1, 5.0 Hz, 2 H, CH_2O), 3.56 (dd, J = 5.1, 5.0 Hz, 2 H, CH_2N), 3.29-3.36 (m, 2 H, CH_2N), 1.43 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR δ 156.0, 149.8, 138.5, 135.9, 130.6, 129.5, 121.6, 117.4, 79.4, 70.3, 68.9, 41.3,

40.3, 28.3 (3); MS (FAB$^+$) m/z 366 (MH$^+$, 40%), 350 (5) 310 (20); HRMS (FAB$^+$) calcd for $C_{16}H_{24}N_5O_5$ (MH$^+$) m/z 366.1777, found 366.1767. Anal. calcd for $C_{16}H_{23}N_5O_5 \cdot ½H_2O$: C, 51.3; H, 6.5; N, 18.7; found: C, 51.3; H, 6.2; N, 16.9%.

3-{[2-(2-Aminoethoxy)ethyl]amino}-1,2,4-benzotriazine 1,4-dioxide (22). Trifluoroacetic acid (1.66 mL, 34.6 mmol) was added dropwise to a stirred solution of 1,4-dioxide **21** (632 mg, 1.73 mmol) in DCM (50 mL) and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between sat. aqueous $KHCO_3$ solution (100 mL) and $CHCl_3$ (100 mL).The aqueous phase was extracted with $CHCl_3$ (8 × 50 mL), the combined organic fractions dried, and the solvent evaporated. The residue was crystallized from $CHCl_3$ to give the amine **22** (406 mg, 91%) as a red solid, mp ($CHCl_3$) 124 °C (dec.); ^{1}H NMR δ 8.26 (d, J = 8.9 Hz, 1 H, H-8), 8.23 (d, J = 8.9 Hz, 1 H, H-5), 7.79 (dd, J = 8.8, 7.8 Hz, 1 H, H-6), 7.45 (dd, J = 8.9, 7.7 Hz, 1 H, H-7), 3.75 (dd, J = 5.0, 4.8 Hz, 2 H, CH_2O), 3.66 (dd, J = 5.0, 4.9 Hz, 2 H, CH_2O), 3.47 (dd, J = 5.1, 5.0 Hz, 2 H, CH_2N), 2.82 (dd, J = 5.1, 5.0 Hz, 2 H, CH_2N), NH and NH_2 not observed; ^{13}C NMR δ 149.8, 138.3, 135.8, 130.5, 127.2, 121.6, 117.4, 73.0, 68.9, 41.7, 41.3; MS (FAB$^+$) m/z 266 (MH$^+$, 20%), 250 (5); HRMS (FAB$^+$) calcd for $C_{11}H_{16}N_5O_3$ (MH$^+$) m/z 266.1253, found 266.1230. Anal. calcd for $C_{11}H_{15}N_5O_3 \cdot ¼H_2O$: C, 49.0; H, 5.8; N, 26.0; found: C, 49.0; H, 5.7; N, 24.7%.

***N*-(2-{2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethoxy}ethyl)-4-acridinecarboxamide (23).** A solution of the amine **22** (54 mg, 0.20 mmol) in THF (2 mL) was added dropwise to a stirred solution of 4-(1*H*-imidazol-1-ylcarbonyl)acridine (58 mg, 0.21 mmol) in THF (5 mL) at 5 °C and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0-5%) of MeOH/DCM, to give compound **23** (93 mg, 97%) as a red solid, mp (EtOAc) 98–100 °C; ^{1}H NMR δ 12.14 (s, 1 H, CONH), 8.96 (dd, J = 7.1, 1.5 Hz, 1 H, H-3'), 8.82 (s, 1 H, H-9), 8.25 (d, J = 8.4 Hz, 1 H, H-8'), 8.16 (d, J = 8.4 Hz, 1 H, H-5'), 8.11–8.13 (m, 2 H, H-1, H-5), 7.94 (d, J = 8.2 Hz, 1 H, H-8), 7.76–7.84 (m, 2 H, H-6, H-6'), 7.66 (dd, J = 8.4, 7.1 Hz, 1 H, H-2), 7.44–7.52 (m, 2 H, H-7, H-7'), 7.36 (br s, 1 H, NH), 3.85–3.95 (m, 8 H, 2 × CH_2O, 2 × CH_2N); ^{13}C NMR δ 166.1, 149.8, 147.2, 146.3, 138.1, 137.6, 135.5, 135.3, 132.4, 131.3, 130.4, 128.8, 128.3, 128.0, 127.1, 126.8, 126.2, 125.8, 125.4, 121.5, 117.3, 70.2, 68.9, 41.1, 39.5; MS

(FAB$^+$) m/z 471 (MH$^+$, 5%), 455 (4); HRMS (FAB$^+$) calcd for $C_{25}H_{23}N_6O_4$ (MH$^+$) m/z 471.1781, found 471.1790. Anal. calcd for $C_{25}H_{22}N_6O_4 \cdot \frac{1}{2}H_2O$: C, 62.6; H, 4.8; N, 17.5; found: C, 63.0; H, 4.7; N, 17.5%.

Example G.

***N*-(2-{2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethoxy}ethyl)-8-quinolinecarboxamide (24).** A solution of 8-quinolinecarboxylic acid (308 mg, 1.78 mmol) and CDI (346 mg, 2.13 mmol) in DMF (20 mL) were stirred at 50 °C for 1 h. The solvent was evaporated and the residue recrystallised from DCM/pet. ether to give 4-(1*H*-imidazol-1-ylcarbonyl)quinoline (50 mg, 0.21 mmol) which was used directly without characterisation. A solution of the amine **22** (57 mg, 0.21 mmol) in DCM (10 mL) was added dropwise to a stirred solution of imidazolide (50 mg, 0.21 mmol) in DCM (5 mL) at 5 °C and the solution was stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give compound **24** (74 mg, 84%) as a red powder, mp (MeOH/DCM) 168–170 °C; ^{1}H NMR δ 11.51 (br s, 1 H, NH), 9.01 (dd, J = 4.2, 1.9 Hz, 1 H, H-2), 8.85 (dd, J = 7.3, 1.6 Hz, 1 H, H-4), 8.30 (d, J = 8.3 Hz, 1 H, H-8"), 8.23–8.26 (m, 2 H, H-7, H-5"), 7.93 (dd, J = 8.1, 1.5 Hz, 1 H, H-5), 7.86 (ddd, J = 8.4, 7.0, 1.8 Hz, 1 H, H-6"), 7.67 (dd, J = 7.9, 7.5 Hz, 1 H, H-6), 7.46–7.51 (m, 2 H, H-3, H-7"), 7.46 (br s, 1 H, NH), 3.78–3.85 (m, 8 H, 2 × CH_2O, 2 × CH_2N); ^{13}C NMR δ 166.0, 149.8, 149.6, 145.6, 138.3, 137.6, 135.7, 133.8, 131.9, 130.5, 128.7, 128.4, 127.2, 126.4, 121.6, 120.9, 117.4, 70.3, 68.9, 41.4, 39.6; MS (FAB$^+$) m/z 421 (MH$^+$, 8%), 405 (5), 389 (1); HRMS (FAB$^+$) calcd for $C_{21}H_{21}N_6O_4$ (MH$^+$) m/z 421.1624, found 421.1615. Anal. calcd for $C_{21}H_{20}N_6O_4 \cdot \frac{1}{2}MeOH$: C, 59.2; H, 5.1; N, 19.3; found: C, 59.2; H, 4.8; N, 19.2%.

Example H.

***N*-(2-{2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethoxy}ethyl)-2-phenyl-1*H*-benzimidazole-4-carboxamide (25).** A solution of 2-phenyl-1*H*-benzimidazole-4-carboxylic acid (396 mg, 1.67 mmol) and CDI (270 mg, 1.67 mmol) in DMF (10 mL) was stirred at 50 °C for 1 h. The solvent was evaporated and the residue recrystallised from DCM/pet. ether to give 4-(1*H*-imidazol-1-ylcarbonyl)-2-phenyl-1*H*-benzimidazole (309 mg, 0.21 mmol) which was used directly without characterisation. A solution of

the amine **22** (56 mg, 0.21 mmol) in DCM (5 mL) was added dropwise to a stirred solution of imidazolide (61 mg, 0.21 mmol) in DCM (5 mL) at 5 °C and the solution was stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give compound **25** (89 mg, 86%) as a red powder, mp (DCM) 203–207 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 13.30 (br s, 1 H, NH), 10.24 (s, 1 H, NH), 8.18–8.24 (m, 3 H, H-2', H-6', NH), 8.13 (d, J = 8.7 Hz, 1 H, H-8''), 8.04 (d, J = 8.5 Hz, 1 H, H-5''), 7.90–7.94 (m, 1 H, H-6''), 7.87 (d, J = 7.9 Hz, 1 H, H-5), 7.72 (d, J = 7.9 Hz, 1 H, H-7), 7.52–7.58 (m, 3 H, H-3', H-5', H-7''), 7.46–7.48 (m, 1 H, H-4'), 7.34 (t, J = 7.9 Hz, 1 H, H-6), 3.78–3.82 (m, 2 H, CH_2O), 3.74–3.77 (m, 2 H, CH_2O), 3.63–3.78 (m, 4 H, 2 × CH_2N); ^{13}C NMR [$(CD_3)_2SO$] δ 164.5, 151.7, 149.7, 141.0, 138.0, 135.4, 135.1, 130.4, 129.9, 128.9 (2), 128.8, 126.9, 126.6 (2), 122.5, 122.3, 122.0, 121.0, 116.7, 114.8, 69.1, 68.2, 40.3, 38.8; MS (FAB$^+$) m/z 486 (MH$^+$, 4%), 470 (2); HRMS (FAB$^+$) calcd for $C_{25}H_{24}N_7O_4$ (MH$^+$) m/z 486.1890, found 486.1903. Anal. calcd for $C_{25}H_{23}N_7O_4$: C, 61.8; H, 4.8; N, 20.2; found: C, 61.6; H, 4.7; N, 20.0%.

Example I.

***N*-(2-{2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethoxy}ethyl)-2-(4-pyridinyl)-8-quinolinecarboxamide (26)**. A solution of 2-(4-pyridinyl)-8-quinolinecarboxylic acid (268 mg, 1.07 mmol) and CDI (173 mg, 1.07 mmol) in DMF (10 mL) were stirred at 50 °C for 1 h. The solvent was evaporated and the residue recrystallized from DCM/pet. ether to give 8-(1*H*-imidazol-1-ylcarbonyl)-2-(4-pyridinyl)quinoline (238 mg, 0.86 mmol) which was used directly without characterization. A solution of the amine **22** (39 mg, 0.15 mmol) in DCM (5 mL) was added dropwise to a stirred solution of imidazolide (41 mg, 0.15 mmol) in DCM (5 mL) at 5 °C and the solution was stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give compound **26** (51 mg, 70%) as a red powder, mp (DCM) 128–130 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.01 (br s, 1 H, NH), 10.83 (t, J = 5.3 Hz, 1 H, NH), 8.70 (dd, J = 4.5, 1.5 Hz, 2 H, H-3', H-5'), 8.63 (d, J = 8.6 Hz, 1 H, H-7), 8.58 (dd, J = 7.3, 1.5 Hz, 1 H, H-4), 8.23 (d, J = 8.7 Hz, 1 H, H-5), 8.19 (dd, J = 8.7, 1.5 Hz, 1 H, H-8''), 8.09 (dd, J = 4.5, 1.5 Hz, 2 H, H-2', H-6'), 7.95 (d, J = 8.5 Hz, 1 H, H-5''), 7.82–7.90 (m, 2 H, H-3, H-6''), 7.76 (t, J = 8.7 Hz, 1 H, H-6), 7.47 (ddd, J = 8.7, 7.0,

1.6 Hz, 1 H, H-7"), 3.70-3.78 (m, 6 H, 2 × CH_2O, CH_2N), 3.49–3.54 (m, 2 H, CH_2N); MS (FAB^+) *m/z* 498 (MH^+, 10%), 482 (5); HRMS (FAB^+) calcd for $C_{26}H_{24}N_7O_4$ (MH^+) *m/z* 498.1890, found 498.1898. Anal. calcd for $C_{26}H_{23}N_7O_4{\cdot}H_2O$: C, 60.7; H, 4.9; N, 22.0; found: C, 60.6; H, 4.9; N, 19.0%.

Example *J*.

***N*-[3-({3-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]-4-acridinecarboxamide (30).**

***tert*-Butyl 3-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]propyl{3-[(trifluoroacetyl)amino]propyl}carbamate (27).** A solution of chloride **3** (1.34 g, 7.41 mmol) in DCM (50 mL) was added dropwise to a stirred solution of *tert*-butyl bis(3-aminopropyl)carbamate (2.57 g, 11.1 mmol) and Et_3N (1.55 mL, 11.1 mmol) in DCM (200 mL) at 20 °C. The solution was stirred at 20 °C for 3 d. The solvent was evaporated and the residue purified by chromatography, eluting with 50% EtOAc/acetone, to give a crude oil (2.31 g). Trifluoroacetic anhydride (3.5 mL, 24.3 mmol) was added dropwise to a stirred solution of crude amine in pyridine (50 mL) at 5 °C. The solution was stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (30–50%) of EtOAc/pet. ether, to give trifluoroacetamide **27** (0.51 g, 22%) as a yellow solid, mp (EtOAc/pet. ether) 89–90 °C; ^{1}H NMR δ 8.22-8.26 (m, 2 H, H-8, NH), 7.71 (br dd, J = 8.4, 7.0 Hz, 1 H, H-6), 7.59 (d, J = 8.4 Hz, 1 H, H-5), 7.29 (br dd, J = 8.5, 7.0 Hz, 1 H, H-7), 5.45 (br s, 1 H, NH), 4.12 (br dd, J = 6.6, 6.5 Hz, 2 H, CH_2N), 3.26–3.37 (m, 6 H, 3 × CH_2N), 1.84–1.95 (m, 2 H, CH_2), 1.71–1.77 (m, 2 H, CH_2), 1.48 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR δ 158.9, 157.3 (q, J = 37 Hz), 156.8, 148.0, 135.6, 130.9, 126.5, 125.1, 120.4, 116 (q, J = 288 Hz), 80.8, 44.5, 43.0, 38.8, 35.8, 29.7, 28.3 (3), 27.1; MS (FAB^+) *m/z* 473 (MH^+, 60%), 457 (10), 373 (100); HRMS (FAB^+) calcd for $C_{20}H_{28}F_3N_6O_4$ (MH^+) *m/z* 473.2124, found 473.2136. Anal. calcd for $C_{20}H_{27}F_3N_6O_4$: C, 50.8; H, 5.8; N, 17.8; found: C, 50.5; H, 5.7; N, 17.8%.

***tert*-Butyl 3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl{3-[(trifluoroacetyl)amino]propyl}carbamate (28).** A solution of MCPBA (2.12 g, 8.6 mmol) in DCM (50 mL) was added dropwise to a stirred solution of 1-oxide **27** (3.13 g, 6.6 mmol) in DCM (250 mL) and $NaHCO_3$ (1.1 g, 13.2 mmol). The mixture was

stirred at 20 °C for 16 h, partitioned between DCM (200 mL) and sat. aqueous $KHCO_3$ solution (100 mL). The organic fraction was dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–4%) of MeOH/40%EtOAc/DCM, to give (i) starting material **27** (2.04 g, 65%) and (ii) 1,4-dioxide **28** (252 mg, 8 %) as a red solid, ^{1}H NMR δ 8.34 (d, J = 8.7 Hz, 1 H, H-8), 8.30 (d, J = 8.4 Hz, 1 H, H-5), 8.25 (br s, 1 H, NH), 7.88 (br dd, J = 8.4, 7.0 Hz, 1 H, H-6), 7.52 (br dd, J = 8.7, 7.0 Hz, 1 H, H-7), 7.20 (br s, 1 H, NH), 3.62 (dt, J = 6.8, 6.7 Hz, 2 H, CH_2N), 3.26–3.38 (m, 6 H, 3 × CH_2N), 1.92–1.98 (m, 2 H, CH_2), 1.73–1.79 (m, 2 H, CH_2), 1.49 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR δ 157.3 (q, J = 37 Hz), 156.8, 149.8, 138.2, 135.9, 130.5, 127.4, 121.7, 117.4, 116.1 (q, J = 288 Hz), 80.9, 44.4, 43.2, 38.9, 31.9, 29.7, 28.4 (3), 22.7; MS (FAB$^+$) m/z 489 (MH$^+$, 10%), 473 (12), 373 (15); HRMS (FAB$^+$) calcd for $C_{20}H_{28}F_3N_6O_5$ (MH$^+$) m/z 489.2073, found 489.2086.

***tert*-Butyl 3-aminopropyl{3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}carbamate (29).** A mixture of trifluoroacetamide **28** (541 mg, 1.11 mmol) and K_2CO_3 (0.77 g, 5.54 mmol) in MeOH (20 mL) and water (5 mL) was heated at reflux temperature for 1 h. The mixture was partitioned between $CHCl_3$ (50 mL) and water (30 mL). The aqueous fraction was extracted with $CHCl_3$ (3 × 30 mL), the combined organic fraction dried, and the solvent evaporated to give amine **29** (322 mg, 74%) as a red oil, ^{1}H NMR [$(CD_3)_2SO$] δ 10.50 (br s, 1 H, NH), 8.21 (d, J = 8.7 Hz, 1 H, H-8), 8.13 (d, J = 8.6 Hz, 1 H, H-5), 7.94 (br dd, J = 8.6, 7.5 Hz, 1 H, H-6), 7.56 (br dd, J = 8.6, 7.5 Hz, 1 H, H-7), 7.20 (br s, 2 H, NH_2), 3.39 (t, J = 6.9 Hz, 2 H, CH_2N), 3.11–3.21 (m, 6 H, 3 × CH_2N), 1.78–1.86 (m, 2 H, CH_2), 1.49–1.58 (m, 2 H, CH_2), 1.39 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR [$(CD_3)_2SO$] δ 154.7, 149.7, 138.1, 135.4, 129.8, 127.9, 121.0, 116.7, 78.3, 44.3, 43.9, 38.8, 38.4, 32.2, 31.6, 27.9 (3); MS (FAB$^+$) m/z 393 (MH$^+$, 15%), 377 (9), 338 (3); HRMS (FAB$^+$) calcd for $C_{18}H_{29}N_6O_4$ (MH$^+$) m/z 393.2250, found 393.2249.

***N*-[3-({3-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]-4-acridinecarboxamide (30).** A solution of 4-acridinecarboxylic acid (846 mg, 4.35 mmol) and CDI (846 mg, 5.21 mmol) in DMF (20 mL) were stirred at 50 °C for 1 h. The solvent was evaporated and the residue recrystallized from DCM/pet. ether to give 4-(1*H*-imidazol-1-ylcarbonyl)acridine (746 mg, 63%) which was used directly

without characterization. A solution of the amine **29** (320 mg, 0.82 mmol) in DCM (10 mL) was added dropwise to a stirred solution of imidazolide (234 mg, 0.86 mmol) in THF (25 mL) at 5 °C and the solution was stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give *tert*-butyl 3-[(4-acridinylcarbonyl)amino]propyl{3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}carbamate (330 mg, 67%) as a red gum, ^{1}H NMR δ 11.92 (br s, 1 H, CONH), 8.98 (dd, J = 7.2, 1.5 Hz, 1 H, H-3), 8.89 (s, 1 H, H-9), 8.26–8.32 (m, 3 H, H-5, H-5', H-8'), 8.16 (d, J = 8.3 Hz, 1 H, H-1), 8.07 (d, J = 8.8 Hz, 1 H, H-8), 7.82–7.89 (m, 3 H, H-3, H-6, H-6'), 7.65–7.69 (m, 1 H, H-7'), 7.58–7.62 (m, 1 H, H-7), 7.48 (br s, 1 H, NH), 3.72 (dt, J = 6.6, 6.0 Hz, 2 H, CH_2N), 3.61 (dt, J = 6.6, 6.4 Hz, 2 H, CH_2N), 3.38–3.50 (m, 4 H, 2 × CH_2N), 2.04–.08 (m, 2 H, CH_2), 1.88-1.94 (m, 2 H, CH_2), 1.40 [s, 9 H, $C(CH_3)_3$]; MS (FAB$^+$) m/z 598 (MH$^+$, 8%), 582 (6); HRMS (FAB$^+$) calcd for $C_{32}H_{36}N_7O_5$ (MH$^+$) m/z 598.2778, found 598.2772.

HCl saturated MeOH (30 mL) was added to a solution of carbamate (328 mg, 0.55 mmol) in MeOH (30 mL) and the solution stirred at 20 °C for 16 h. The solution was evaporated and the residue dissolved in water (20 mL) the solution neutralized with $KHCO_3$ and extracted with $CHCl_3$ (5 × 50 mL). The combined organic fraction was dried and the solvent evaporated to give compound **30** (247 mg, 90%) as a red solid, ^{1}H NMR [$(CD_3)_2SO$] δ 11.38 (t, J = 5.5 Hz, 1 H, CONH), 10.50 (br s, 1 H, NH), 9.28 (s, 1 H, H-9), 8.71 (dd, J = 7.1, 1.5 Hz, 1 H, H-3), 8.35 (dd, J = 8.4, 1.5 Hz, 1 H, H-1), 8.24 (d, J = 8.7 Hz, 1 H, H-5), 8.19 (d, J = 8.3 Hz, 1 H, H-8), 8.14 (d, J = 8.5 Hz, 1 H, H-8'), 8.03 (d, J = 8.5 Hz, 1 H, H-5'), 7.92–7.96 (m, 1 H, H-6), 7.83–7.88 (m, 1 H, H-6'), 7.75 (dd, J = 8.3, 7.1 Hz, 1 H, H-2), 7.65–7.68 (m, 1 H, H-7), 7.48–7.54 (m, 1 H, H-7'), 7.38 (s, 1 H, NH), 3.64 (dt, J = 6.9, 5.9 Hz, 2 H, CH_2N), 3.46 (t, J = 6.7 Hz, 2 H, CH_2N), 2.79 (t, J = 6.9 Hz, 2 H, CH_2N), 2.70 (t, J = 6.5 Hz, 2 H, CH_2N), 1.88–1.94 (m, 2 H, CH_2), 1.76–1.82 (m, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 164.7, 149.6, 147.0, 145.4, 138.5, 138.0, 135.3, 134.4, 132.6, 131.8, 129.7, 128.5, 128.4, 128.3, 126.7, 1264.4, 126.3, 125.5, 125.2, 121.0, 116.7, 47.1, 46.9, 39.6, 37.2, 29.3, 28.2; MS (FAB$^+$) m/z 498 (MH$^+$, 15%), 482 (5); HRMS (FAB$^+$) calcd for $C_{27}H_{28}N_7O_3$ (MH$^+$) m/z 498.2254, found 498.2258. Anal. calcd for $C_{27}H_{27}N_7O_3 \cdot 2H_2O$: C, 60.8; H, 5.9; N, 18.4; found: C, 60.7; H, 5.6; N, 17.1%.

Example K.

***N*-[3-({3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]-1-phenazinecarboxamide hydrochloride (31).** A solution of the amine **29** (223 mg, 0.57 mmol) in THF (10 mL) was added dropwise to a stirred solution of 1-(1*H*-imidazol-1-ylcarbonyl)phenazine (171 mg, 0.63 mmol) in THF (25 mL) at 5 °C and the solution was stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–3%) of MeOH/DCM, to give *tert*-butyl 3-[(1-phenazinecarbonyl)amino]propyl{3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}carbamate (137 mg, 40%) as a red gum, ^{1}H NMR δ 11.22 and 11.06 (2 × s, 1 H, CONH), 9.03 (dd, J = 7.1, 1.4 Hz, 1 H, H-2), 8.64 and 8.27 (2 × s, 1 H, NH), 8.42 (d, J = 8.2 Hz, 1 H, H-9), 8.29–8.37 (m, 3 H, H-4, H-6, H-8'''), 7.86–8.03 (m, 5 H, H-3, H-7, H-8, H-5''', H-6'''), 7.49–7.56 (m, 1 H, H-7'''), 3.69–3.77 (m, 2 H, CH_2N), 3.63–3.68 (m, 2 H, CH_2N), 1.93–2.10 (m, 4 H, 2 × CH_2N), 1.67 and 1.63 [2 × s, 9 H, $C(CH_3)_3$], 1.45–1.53 (m, 4 H, 2 × CH_2); MS (FAB$^+$) *m/z* 599 (MH$^+$, 12%), 583 (3); HRMS (FAB$^+$) calcd for $C_{31}H_{35}N_8O_5$ (MH$^+$) *m/z* 599.2730, found 599.2733. HCl saturated MeOH (5 mL) was added to a solution of carbamate (135 mg, 0.23 mmol) in MeOH (20 mL) and the solution stirred at 20 °C for 16 h. The solution was evaporated and the residue dissolved in water (20 mL) the solution neutralized with dil. aqueous NH_3 and extracted with $CHCl_3$ (5 × 50 mL). The combined organic fraction was dried and the solvent evaporated to give compound **31** (97 mg, 85%) as a red solid, which was converted to the HCl salt and recrystallized, mp (MeOH/EtOAc) 163–169 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.29 (t, J = 5.8 Hz, 1 H, CONH), 9.26 (br s, 2 H, $NH_2^+Cl^-$), 8.97 (t, J = 6.1 Hz, 1 H, NH), 8.59 (dd, J = 9.0, 2.0 Hz, 1 H, H-2), 8.55 (dd, J = 9.0, 2.0 Hz, 1 H, H-9), 8.41 (dd, J = 8.7, 1.3 Hz, 1 H, H-4), 8.28 (dd, J = 7.9, 2.0 Hz, 1 H, H-6), 8.19 (d, J = 8.2 Hz, 1 H, H-8'''), 7.98–8.08 (m, 5 H, H-3, H-7, H-8, H-5''', H-6'''), 7.60 (ddd, J = 8.7, 7.1, 1.4 Hz, 1 H, H-7'''), 3.65–3.69 (m, 2 H, H'), 3.55–3.59 (m, 2 H, H-3''), 3.04–3.13 (m, 4 H, H-3', H-1''), 2.03–2.15 (m, 4 H, H-2', H-2''); ^{13}C NMR [$(CD_3)_2SO$] δ 164.8, 149.8, 142.6, 142.5, 141.3, 139.9, 137.5, 136.5, 133.4, 132.6, 131.8, 131.6, 131.0, 130.5, 130.2, 129.5, 129.0, 127.5, 121.8, 116.2, 44.6, 44.2, 38.1, 36.4, 25.9, 25.1. Anal. calcd for $C_{26}H_{27}ClN_8O_3 \cdot MeOH$: C, 57.2; H, 5.5; N, 19.8; found: C, 57.3; H, 5.8; N, 20.0%.

Example L

N-[3-({3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]-9-methyl-1-phenazinecarboxamide hydrochloride (32). A solution of the amine **29** (265 mg, 0.68 mmol) in THF (10 mL) was added dropwise to a stirred solution of 1-(1*H*-imidazol-1-ylcarbonyl)-9-methylphenazine (214 mg, 0.74 mmol) in THF (25 mL) at 5 °C and the solution was stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (5–10%) of MeOH/DCM, to give *tert*-butyl 3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl(3-{[(9-methyl-1-phenazinyl)carbonyl]amino}propyl)carbamate (168 mg, 40%) as a red gum, MS (FAB$^+$) m/z 613 (MH$^+$, 20%), 597 (5), 513 (15), 497 (5); HRMS (FAB$^+$) calcd for C32H37N_8O_5 (MH$^+$) m/z 613.2887, found 613.2881.
HCl saturated MeOH (5 mL) was added to a solution of carbamate (168 mg, 0.27 mmol) in MeOH (20 mL) and the solution stirred at 20 °C for 16 h. The solution was evaporated and the residue dissolved in water (20 mL) the solution neutralized with dil. aqueous NH_3 and extracted with $CHCl_3$ (5 × 50 mL). The combined organic fraction was dried and the solvent evaporated to give compound **32** (121 mg, 86%) as a red solid, which was converted to the HCl salt and recrystallized, mp (MeOH/EtOAc) 183–186 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.45 (t, J = 5.8 Hz, 1 H, CONH), 9.18 (br s, 2 H, $NH_2^+Cl^-$), 8.73 (t, J = 6.2 Hz, 1 H, NH), 8.63 (dd, J = 7.0, 1.4 Hz, 1 H, H-2), 8.39 (dd, J = 8.7, 1.4 Hz, 1 H, H-4), 8.18 (d, J = 8.7 Hz, 1 H, H-8'''), 8.03–8.11 (m, 3 H, H-3, H-5''', H-7), 7.92 (ddd, J = 8.5,7.1, 1.3 Hz, 1 H, H-6'''), 7.87–7.93 (m, 2 H, H-6, H-8), 7.57 (ddd, J = 8.7, 7.1, 1.3 Hz, 1 H, H-7'''), 3.61–3.66 (m, 2 H, H'), 3.51–3.57 (m, 2 H, H-3''), 2.98–3.10 (m, 4 H, H-3', H-1''), 2.86 (s, 3 H, CH_3), 2.08–2.15 (m, 2 H, H-2'), 1.99–2.05 (m, 2 H, H-2''); ^{13}C NMR [$(CD_3)_2SO$] δ 164.5, 149.7, 142.6, 142.3, 140.4, 138.7, 137.7, 136.6, 136.0, 133.7, 132.7, 131.5, 131.2, 130.2, 130.1, 130.0, 127.1, 127.0, 121.0, 116.4, 44.8, 44.7, 37.9, 36.6, 26.2, 25.1, 17.5; MS (FAB$^+$) m/z 513 (MH$^+$, 20%), 497 (5); HRMS (FAB$^+$) calcd for $C_{27}H_{29}N_8O_3$ (MH$^+$) m/z 513.2363, found 513.2352.

Example M

N-[2-({2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethyl}amino)ethyl]-4-acridinecarboxamide (37).

***tert*-Butyl bis-(2-aminoethyl)carbamate (33).** Diethylenetriamine (9.9 mL, 96 mmol) was added to a solution of CF_3CO_2Et (22.8 mL, 192 mmol) in dry ether (80

mL) at 5 °C and the reaction mixture was stirred at 20 °C for 20 h. The resulting white precipitate was filtered and washed with cold ether (100 mL), dried under vacuum to give 2,2,2-trifluoro-*N*-[2-({2-[(trifluoroacetyl)amino]ethyl}amino)ethyl]acetamide (17.26 g, 61%), ^{1}H NMR [$(CD_3)_2SO$] δ 7.26 (br, 2 H, 2 × CONH), 3.43 (br s, 4 H, 2 × CH_2), 2.86 (t, J = 5.8 Hz, 4 H, 2 × CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 157.7 (q, J = 37 Hz), 115.8 (q, J = 288 Hz), 47.3 (2), 39.3 (2).

Di-*tert* butyldicarbonate (8.26 g, 37.8 mmol) was added to a solution of acetamide (10.15 g, 34.4 mmol) in THF (100 mL) at 0 °C and the mixture was stirred at 20 °C for 20 h. Saturated aqueous NH_4Cl (80 mL) added and the mixture stirred at 20 °C for 5 h. The mixture was extracted with DCM (3 × 50 mL), dried, and the solvent evaporated to give *tert*-butyl bis{2-[(trifluoroacetyl)amino]ethyl}carbamate (13.5 g, 100 %), ^{1}H NMR [$(CD_3)_2SO$] δ 9.47 (br, 1 H, CONH), 9.40 (br, 1 H, CONH), 3.30 (m, 8 H, 4 × CH_2), 1.38 [s, 9H, $C(CH_3)_3$]; ^{13}C NMR [$(CD_3)_2SO$] δ 156.4 (q, J = 36 Hz), 154.7, 115.8 (q, J = 288 Hz), 78.9, 45.4, 45.0, 37.7, 37.4, 27.7 (3).

Conc. ammonia (50 mL) was added to a solution of carbamate (14.0 g, 35.5 mmol) in MeOH (100 mL) and heated at reflux temperature for 20 hr. The solvent was evaporated to give diamine **33** as a yellow foam, ^{1}H NMR [$(CD_3)_2SO$] δ 3.39 (t, J = 6.4 Hz, 4 H, 2 × CH_2), 2.94 (t, J = 6.4 Hz, 4 H, 2 × CH_2), 1.42 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR [$(CD_3)_2SO$] δ 154.9, 79.9, 45.1 (2), 37.4 (2), 27.9 (3).

Di-*tert*-butyl 2-aminoethyl{2-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]ethyl}dicarbamate (35). A solution of chloride **3** (1.0 g, 5.5 mmol), diamine **33** (4.47 g, 22.0 mmol), and Et_3N (2.24 g, 22 mmol) in DME (20 mL) was heated at 90 °C for 3 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–4%) of MeOH/DCM to give (i) *tert*-butyl bis{2-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]ethyl}carbamate (0.34 g, 25%), ^{1}H NMR δ 8.17 (br d, J = 8.5 Hz, 2 H, H-8), 7.71–7.62 (m, 2 H, H-6), 7.52 (br d, J = 8.3 Hz, 2 H, H-8), 7.26-7.22 (m, 2 H, H-7), 6.15 (br s, 1 H, NH), 5.95 (br s, 1 H, NH), 3.71 (br q, J = 5.8 Hz, 4 H, 2 × CH_2), 3.37 (br s, 4 H, 2 × CH_2), 1.50 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR δ 158.9, 156.3 (2), 148.6 (2), 135.5 (2), 130.9 (2), 126.4 (2), 124.9 (2), 120.3 (2), 80.7, 47.7 (2), 40.9 (2), 28.4 (3); and (ii) crude *tert*-butyl 2-aminoethyl{2-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]ethyl}carbamate **34** (1.38 g, 72 %) as a yellow foam.

Di-*tert*-butyldicarbonate (2.7 g, 12.4 mmol) was added to a solution of carbamate **34** (1.38 g, 4.0 mmol) in THF (50 mL) and the solution stirred at 20 °C for 36 h. Water (100 mL) was added and the mixture stirred at 20 °C for 1 h. The mixture was extracted with DCM (3 × 50 mL), the organic fraction dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(0–7%) MeOH/DCM, to give carbamate **35** (0.94 g, 52 %) as a yellow powder, mp (DCM/hexane) 160–163 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.14 (dd, J = 8.3, 0.7 Hz, 1 H, H-8), 8.00 and 7.92 (2 × br s, 1 H, CONH), 7.79 (dd, J = 7.5, 1.2 Hz, 1 H, H-6), 7.58 (br d, J = 7.5 Hz, 1 H, H-5), 7.34 (dd, J = 7.7, 1.2 Hz, 1 H, H-7), 6.81 (br s, 1 H, NH), 3.43–3.47 (m, 2 H, CH_2), 3.37 (m, 2 H, CH_2), 3.22 (t, J = 6.2 Hz, 2 H, CH_2), 3.03-3.07 (m, 2 H, CH_2), 1.34 [s, 9 H, $C(CH_3)_3$], 1.34 and 1.27 [2 × s, 9 H, $C(CH_3)_3$]; ^{13}C NMR [$(CD_3)_2SO$] δ 158.9, 155.5, 154.7,148.2, 135.7, 130.1, 126.0, 124.6, 119.8, 78.4, 77.5, 47.0, 46.2, 38.5, 38.1, 28.1(3), 27.8 (3). Anal. calcd for $C_{21}H_{32}N_6O_5$ C, 56.2; H, 7.2; N, 18.7; found C, 56.5; H, 7.5; N, 18.8%.

Di-*tert*-butyl 2-aminoethyl{2-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]ethyl}dicarbamate (36). MCPBA (247 mg, 1.0 mmol) was added to a solution of 1-oxide **35** (300 mg, 0.67 mmol) in DCM (10 mL) and the mixture was stirred at 20 °C for 16 h. The mixture was partitioned between dil. aqueous NH_3 (50 mL) and DCM (50 mL) and the aqueous fraction extracted with DCM (3 × 30 mL). The combined organic fraction was dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–2%) of MeOH/DCM, to give (i) starting material (188 mg, 62%) and (ii) 1,4-dioxide **36** (122 mg 39%), mp (DCM/hexane) 128-134 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.39 and 8.32 (2 × br s, 1 H, CONH), 8.21 (dd, J = 8.7, 0.7 Hz, 1 H, H-8), 8.14 (t, J = 8.0 Hz, 1 H, H-5), 7.94 (t, J = 7.6 Hz, 1 H, H-6), 7.57 (t, J = 7.9 Hz, 1 H, H-7), 6.77 (br s, 1 H, NH), 3.50–3.54 (m , 2 H, CH_2), 3.41-3.44 (m, 2 H, CH_2), 3.20 (t, J = 6.5 Hz, 2 H, CH_2), 3.03 (br q, J = 5.6 Hz, 2 H, CH_2), 1.33 [s, 9 H, $C(CH_3)_3$], 1.33 and 1.26 [2 × s, 9 H, $C(CH_3)_3$]; ^{13}C NMR [$(CD_3)_2SO$] δ 155.5 154.6, 149.8, 138.1, 135.5, 129.9, 127.0, 121.0, 116.81, 78.6, 77.4, 46.8, 46.1, 38.5, 38.0, 28.8, 27.7; HRMS calcd for $C_{21}H_{33}H_6O_6$ (M^+) *m/z* 465.2462, found 465.2456.

***N*-[2-({2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethyl}amino)ethyl]-4-acridinecarboxamide (37).** A solution of carbamate **36** (252 mg, 0.54 mmol) in HCl saturated MeOH (10 mL) was stirred at 20 °C for 24 h. The solvent was evaporated and the residue partitioned between aqueous NH_3 (20 mL) and DCM (50 mL). The aqueous fraction was extracted with DCM (5 × 20 mL) and the combined organic extracts dried. The solvent was evaporated to give N^1-(2-aminoethyl)-N^2-(1,4-dioxido-1,2,4-benzotriazin-3-yl)-1,2-ethanediamine (109 mg, 76%), ^{1}H NMR δ 8.33 (d, J = 8.7 Hz, 1 H, H-8), 8.30 (d, J = 8.8 Hz, 1 H, H-5), 7.87 (ddd, J = 8.5, 7.1, 1.0 Hz, 1 H, H-6), 7.50 (ddd, J = 8.4, 7.1, 1.2 Hz, 1 H, H-7), 3.70 (t, J = 5.9 Hz, 2 H, CH_2), 2.98 (t, J = 5.9 H, 2 H, CH_2), 2.84 (t, J = 5.6 Hz, 2 H, CH_2), 2.74 (t, J = 5.6 Hz, 2 H, CH_2), 2 × NH and NH_2 not observed.

A solution of N^1-(2-aminoethyl)-N^2-(1,4-dioxido-1,2,4-benzotriazin-3-yl)-1,2-ethanediamine (96 mg, 0.36 mmol) and 4-(1*H*-imidazol-1-ylcarbonyl)acridine (119 mg, 0.43 mmol) in DMF (5 mL) was stirred at 20 °C for 5 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–2%) of aqueous NH_3/(0–7%) MeOH/DCM, to give compound **37** (168 mg, 99%) as a red solid, mp (DCM/hexane) 151–154 °C; ^{1}H NMR δ 11.98 (t, J = 5.3 Hz, 1 H, CONH), 8.82 (dd, J = 8.2, 1.4 Hz, 1 H, ArH), 8.81 (s, 1 H, ArH), 8.08–8.17 (m, 4 H, 4 × ArH), 7.97 (d, J = 8.3 Hz, 1 H, ArH), 7.75–7.82 (m, 2 H, 2 × ArH), 7.60 (dd, J = 8.2, 7.2 Hz, 1 H, ArH), 7.54 (ddd, J = 8.3, 7.3, 0.9 Hz, 1 H, ArH), 7.40 (ddd, J = 8.6, 7.2, 1.2 Hz, 1 H, ArH), 3.86 (br q, J = 5.8 Hz, 2 H, CH_2), 3.70 (t, J = 5.8 Hz, 2 H, CH_2), 3.17 (br q, J = 6.3 Hz, 4 H, 2 × CH_2), 2 × NH not observed; ^{13}C NMR δ 166.5, 149.7, 147.4, 146.2, 138.0, 137.7, 135.6, 135.3, 132.5, 131.4, 130.2, 128.9, 128.0, 126.9 (2), 126.7, 126.3, 125.9, 125.4, 121.5, 117.2, 48.6, 47.8, 40.6, 39.3; HRMS (FAB^+) calcd for $C_{25}H_{24}N_7O_3$ (MH^+) m/z 470.1941 found 470.1934. Anal. calcd for $C_{25}H_{23}N_7O_3 \cdot 1\frac{1}{2}H_2O$: C, 60.5; H, 5.3; N, 19.8; found C, 60.5; H, 5.0; N, 20.0%.

Example N

***N*-{3-[{3-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}(methyl)amino]propyl}-4-acridinecarboxamide (41).**

2,2,2-Trifluoro-*N*-[3-(methyl{3-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]acetamide (38). A solution of chloride **3** (2.07 g, 11.4 mmol), N^1-(3-aminopropyl)-N^1-methyl-1,3-propanediamine (3.31 g, 22.8 mmol)

and Et_3N (3.2 mL, 22.8 mmol) in DCM (200 mL) was stirred at 20 °C for 2 d. The solvent was evaporated and the residue dissolved in MeCN (150 mL). Ethyl trifluoroacetate (5.4 mL, 45.6 mmol) and water (0.8 mL, 45.6 mmol) added and the solution heated at reflux temperature for 16 h. The solvent was evaporated, and the residue purified by chromatography, eluting with a gradient (0–1%) of Et_3N/(0–10%) MeOH/DCM, followed by further chromatography, eluting with 10% MeOH/DCM, to give 1-oxide **38** (1.89 g, 43%) as a yellow solid, mp (DCM) 111–115 °C; ^{1}H NMR δ 9.04 (br s, 1 H, NH), 8.25 (dd, J = 8.7, 1.4 Hz, 1 H, H 8'), 7.70 (ddd, J = 8.4, 7.1, 1.4 Hz, 1 H, H-6'), 7.57 (d, J = 8.4 Hz, 1 H, H-5'), 7.29 (ddd, J = 8.7, 7.1, 1.1 Hz, 1 H, H-7'), 6.17 (br s, 1 H, NH), 3.58 (dd, J = 6.6, 5.8 Hz, 2 H, CH_2N), 3.49 (br t, J = 6.0 Hz, 2 H, CH_2N), 2.52–2.58 (m, 4 H, 2 × CH_2N), 2.27 (s, 3 H, NCH_3), 1.84–1.90 (m, 2 H, CH_2), 1.75–1.82 (m, 2 H, CH_2); ^{13}C NMR δ 158.9, 157.3 (q, J = 36 Hz), 148.8, 135.6, 130.8, 126.4, 124.9, 120.4, 116.1 (q, J = 288 Hz), 57.1, 56.4, 41.3, 40.3 (2), 26.3, 24.4; MS (FAB$^+$) m/z 387 (MH$^+$, 100%), 371 (8), 338 (30); HRMS (FAB$^+$) calcd for $C_{16}H_{22}F_3N_6O_2$ (MH$^+$) m/z 387.1756, found 387.1765. Anal. calcd for $C_{16}H_{21}F_3N_6O_2$•½MeOH: C, 49.2; H, 5.8; N, 20.9; found: C, 49.1; H, 5.5; N, 20.7%.

***N*-{3-[{3-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}(methyl)amino]propyl}-2,2,2-trifluoroacetamide (39).**

Trifluoroacetic anhydride (4.13 mL, 29.2 mmol) was added to a stirred solution of 1-oxide **38** (1.13 g, 2.92 mmol) in $CHCl_3$ (50 mL) and the solution stirred at 20 °C for 30 min. The solution was cooled to –10 °C and 70% H_2O_2 (2 mL) (CAUTION) added dropwise. The solution was stirred at 20 °C for 30 d, partitioned between $CHCl_3$ (50 mL) and sat. aqueous $KHCO_3$ (50 mL). The aqueous fraction was extracted with $CHCl_3$ (3 × 30 mL), the combined organic fraction dried and the solvent evaporated (CAUTION: safety shield). The residue was purified by chromatography, eluting with 10% MeOH/DCM, to give (i) starting material **38** (275 mg, 24%) and (ii) 1,4-dioxide **39** (319 mg, 27%) as a red gum, ^{1}H NMR [$(CD_3)_2SO$] δ 9.44 (br s, 1 H, NH), 8.45 (t, J = 5.9 Hz, 1 H, NH), 8.20 (d, J = 8.8 Hz, 1 H, H-8'), 8.12 (d, J = 8.6 Hz, 1 H, H-5'), 7.93 (ddd, J = 8.6, 7.1, 1.2 Hz, 1 H, H-6'), 7.57 (ddd, J = 8.8, 7.1, 1.3 Hz, 1 H, H-7'), 3.42–3.47 (m, 2 H, CH_2N), 3.21–3.25 (m, 2 H, CH_2N), 2.39 (t, J = 6.7 Hz, 2 H, CH_2N), 2.32 (t, J = 6.9 Hz, 2 H, CH_2N), 2.16 (s, 3 H, NCH_3), 1.72–1.80 (m, 2 H, CH_2), 1.61–1.68 (m, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 155.9 (q, J = 36 Hz), 149.7,

138.1, 135.4, 129.8, 126.7, 121.0, 116.7, 115.9 (q, J = 288 Hz), 54.9, 54.6, 41.4, 39.5, 37.6, 25.9, 25.8; MS (FAB$^+$) m/z 403 (MH$^+$, 25%), 387 (5); HRMS (FAB$^+$) calcd for $C_{16}H_{22}F_3N_6O_3$ (MH$^+$) m/z 403.1706, found 403.1695.

N-{3-[{3-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}(methyl)amino]propyl}-4-acridinecarboxamide (41). A solution of trifluoroacetamide **39** (175 mg, 0.44 mmol) and NH_4OH (5 mL) in MeOH (20 mL) was stirred at 30 °C for 4 h. The solvent was evaporated and the residue dried to give N^1-(3-aminopropyl)-N^3-(1,4-dioxido-1,2,4-benzotriazin-3-yl)-N^1-methyl-1,3-propanediamine (**40**) as a red gum, ^{1}H NMR [$(CD_3)_2SO$] δ 8.43 (br s, 1 H, NH), 8.21 (d, J = 8.5 Hz, 1 H, H-8'), 8.13 (d, J = 8.4 Hz, 1 H, H-5'), 7.94 (ddd, J = 8.4, 7.1, 1.2 Hz, 1 H, H-6'), 7.75 (br s, 2 H, NH_2), 7.57 (ddd, J = 8.7, 7.2, 1.3 Hz, 1 H, H-7'), 3.45 (t, J = 6.8 Hz, 2 H, CH_2N), 3.20–3.25 (m, 2 H, CH_2N), 2.88 (dd, J = 7.4, 7.2 Hz, 2 H, CH_2N), 2.40–2.46 (m, 2 H, CH_2N), 2.20 (s, 3 H, NCH_3), 1.77–1.83 (m, 2 H, CH_2), 1.68–1.75 (m, 2 H, CH_2); MS (FAB$^+$) m/z 307 (MH$^+$, 2%), 291 (5); HRMS (FAB$^+$) calcd for $C_{14}H_{23}N_6O_3$ (MH$^+$) m/z 307.1883, found 307.1883. The amine **40** was dissolved in DCM (5 mL) and added to a stirred solution of 4-(1H-imidazol-1-ylcarbonyl)acridine (125 mg, 0.46 mmol) in THF (20 mL) and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–1%) of Et_3N/(0–15%) MeOH/DCM, to give compound **41** (146 mg, 66%) as a red solid, mp (EtOAc/DCM) 169–171 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.41 (t, J = 5.3 Hz, 1 H, CONH), 9.31 (s, 1 H, H-9), 8.69 (dd, J = 7.0, 1 4 Hz, 1 H, H-3), 8.43 (t, J = 5.6 Hz, 1 H, NH), 8.38 (d, J = 7.4 Hz, 1 H, H-1), 8.32 (d, J = 8.8 Hz, 1 H, H-5), 8.21 (d, J = 8.4 Hz, 1 H, H-8), 8.16 (d, J = 8.7 Hz, 1 H, H-8'), 8.09 (d, J = 8.7 Hz, 1 H, H-5'), 7.96 (ddd, J = 8.7, 7.1, 1.1 Hz, 1 H, H-6'), 7.91 (dd, J = 8.8, 7.5 Hz, 1 H, H-6), 7.74 (dd, J = 7.4, 7.0 Hz, 1 H, H-2), 7.69 (br dd, J = 8.7, 7.1 Hz, 1 H, H-7'), 7.55 (dd, J = 8.4, 7.5 Hz, 1 H, H-7), 3.60–3.65 (m, 2 H, CH_2N), 3.42–3.48 (m, 2 H, CH_2N), 3.39 (s, 3 H, NCH_3), 3.00–3.08 (m, 2 H, CH_2N), 2.60–2.68 (m, 2 H, CH_2N), 2.02–2.08 (m, 2 H, CH_2), 1.92–1.98 (m, 2 H, CH_2); MS (FAB$^+$) m/z 512 (MH$^+$, 25%), 496 (10); HRMS (FAB$^+$) calcd for $C_{28}H_{30}N_7O_3$ (MH$^+$) m/z 512.2410, found 512.2424.

Example O.

***N*-{3-[{3-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}(methyl)amino]propyl}-8-quinolinecarboxamide (42).** A solution of 8-quinolinecarboxylic acid (90 mg, 0.5 mmol) and CDI (97 mg, 0.6 mmol) in DMF (5 mL) was stirred at 55 °C for 24 h. The solution was diluted with dry benzene (10 mL), Sephadex LH-20 (300 mg) was added and the mixture stirred at 20 °C for 1 h. The mixture was filtered and the solvent evaporated. The residue was dissolved in dry THF (5 mL) and a solution of (**40**) (80 mg, 0.25 mmol) in THF (5 mL) added, and the solution stirred at 20 °C for 70 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–2%) of aqueous NH_3/(0–8%) MeOH/DCM, to give compound **42** (110 mg, 91%) as a red powder, mp (DCM/pet. ether) 119–121 °C; ^{1}H NMR δ 11.39 (br s, 1 H, CONH), 8.96 (dd, J = 4.3, 1.8 Hz, 1 H, ArH), 8.74 (dd, J = 7.3, 1.5 Hz, 1 H, ArH), 8.34 (dd, J = 8.8, 1.8 Hz, 1 H, ArH), 8.25 (d, J = 8.3 Hz, 1 H, ArH), 8.17 (d, J = 8.6 Hz, 1 H, ArH), 7.98 (br s, 1 H, NH), 7.92 (dd, J = 8.1, 1.5 Hz, 1 H, ArH), 7.78 (dd, J = 8.1, 1.1 Hz, 1 H, ArH), 7.62 (t, J = 7.7 Hz, 1 H, ArH), 7.48 (dd, J = 8.3, 1 H, 4.0 Hz), 7.43 (dd, J = 7.9, 1.0 Hz, 1 H, ArH), 3.68–3.73 (m, 4 H, 2 × CH_2), 3.05 (br m, 4 H, 2 × CH_2), 2.67 (s, 3 H, CH_3), 2.25-2.17 (m, 4 H, 2 × CH_2); ^{13}C NMR δ 166.4, 149.7, 149.6, 145.4, 138.2, 137.7, 135.6, 133.6, 132.0, 130.3, 128.5, 128.4, 127.1, 126.4, 121.5, 121.0, 117.3, 54.7, 54.5, 40.6, 39.4, 37.2, 25.5, 24.5; MS (FAB$^+$) m/z 462 (MH$^+$, 25%), 446 (5); HRMS calcd for $C_{24}H_{28}N_7O_3$ (MH$^+$) m/z 462.2254, found 462.2249. Anal. calcd for $C_{24}H_{27}N_7O_3$: C, 62.5; H, 5.9; N, 21.2; found: C, 62.1; H, 6.0 ; N, 21.2%.

Example P.

***N*-{3-[{3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}(methyl)amino]-propyl}-2-(4-pyridyl)-8-quinolinecarboxamide (43).** A solution of 2-(4-pyridyl)-quinoline-8-carboxylic acid (160 mg, 0.62 mmol) and CDI (150 mg, 0.92 mmol) in DMF (10 mL) was stirred at 55 °C for 24 h. The solution was cooled to 20 °C, diluted with dry benzene (15 mL), Sephadex LH-20 (300 mg) was added and the mixture stirred at 20 °C for 1 h. The mixture was filtered and the solvent evaporated. The residue was dissolved in dry THF (5 mL) and a solution of (39) (90 mg, 0.33 mmol) in THF (5 mL) added, and the solution stirred at 20 °C for 4 days. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–2%) of aqueous NH_3/(0–8%) MeOH/DCM, to give compound **43** (160 mg, 94%) as a

red powder, mp (DCM/pet. ether) 179–181 °C; ^{1}H NMR δ 11.08 (br s, 1 H, CONH), 8.86 (dd, J = 4.5, 1.6 Hz, 2 H, ArH), 8.78 (dd, J = 7.4, 1.5 Hz, 1 H, ArH), 8.37 (d, J = 8.6 Hz, 1 H, ArH), 8.21 (d, J = 8.6 Hz, 1 H, ArH), 8.10 (d, J = 8.6 Hz, 1 H, ArH), 7.95 (dd, J = 8.2, 1.4 Hz, 1 H, ArH), 7.92–7.90 (m, 4 H, NH, 3 × ArH), 7.98 (ddd, J = 8.6, 7.5, 1.3 Hz, 1 H, ArH), 7.66 (t, J = 7.7 Hz, 1 H, ArH) 7.40 (ddd, J = 8.6, 7.2, 1.2 Hz, 1 H, ArH), 3.74 (br q, J = 6.4 Hz, 2 H, CH_2), 3.61 (br m, 2 H, CH_2), 2.85 (br m, 2 H, CH_2), 2.81 (br m, 2 H, CH_2), 2.45 (s, 3 H, CH_3), 2.17 (br q, J = 7.2 Hz, 2 H, CH_2), 1.98 (br m, 2 H, CH_2); ^{13}C NMR δ 166.1, 154.5, 150.9, 149.7, 146.2, 145.3, 139.0, 138.2, 135.5, 134.4, 131.5, 130.2, 129.4, 127.9, 127.2, 126.9,121.7, 121.5, 118.7, 117.2, 55.3, 55.2, 41.0, 40.1, 37.7, 26.6, 24.7; HRMS (FAB^+) calcd for $C_{29}H_{31}N_8O_3$ (MH^+) m/z 539.2519, found 539.2527. Anal. calcd for $C_{29}H_{30}N_8O_3\cdot\frac{1}{2}H_2O$: C, 64.7; H, 5.6; N, 20.8; found: C, 64.1; H, 5.7; N, 20.6%.

Example Q.

***N*-{3-[{3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}(methyl)amino]-propyl}-5-methyl-4-acridinecarboxamide (44).** A solution of 5-methylacridine-4-carboxylic acid (0.13 g, 0.55 mmol) and CDI (0.21 g, 1.3 mmol) in DMF (5 mL) was stirred at 55 °C for 24 h. The solution was diluted with dry benzene (10 mL), Sephadex LH-20 (300 mg) was added and the mixture stirred at 20 °C for 1 h. The mixture was filtered and the solvent evaporated. The residue was dissolved in dry THF (5 mL) and a solution of **40** (80 mg, 0.27 mmol) in THF (5 mL) added, and the solution stirred at 20 °C for 70 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–2%) of aqueous NH_3/(0–8%) MeOH/DCM, to give compound **44** (0.13 g, 88%) as a red powder, mp (DCM/pet. ether) 158-162 °C; ^{1}H NMR δ 12.08 (br s, 1 H, CONH), 8.83 (d, J = 6.9 Hz, 1 H, ArH), 8.76 (s, 1 H, NH), 8.06 (t, J = 8.9 Hz, 2 H, ArH), 7.97 (br d, J = 8.4 Hz, 2 H, ArH), 7.83 (d, J = 8.4 Hz, 1 H, ArH), 7.66 (d, J = 6.7 Hz, 1 H, ArH), 7.56-7.63 (m, 2 H, ArH), 7.46 (dd, J = 7.6, 6.5 Hz, 1 H, ArH), 7.30 (d, J = 7.9 Hz, 1 H, ArH), 3.77 (br q, J = 6.3 Hz, 2 H, CH_2), 4.83 (br m, 2 H, CH_2), 3.08 (br m, 4 H, 2 × CH_2), 2.83 (s, 3 H, CH_3), 2.67 (br s, 3 H, CH_3), 2.31 (br m, 2 H, CH_2), 2.15 (br m, 2 H, CH_2); ^{13}C NMR δ 166.5, 149.6, 146.9, 145.1, 137.9, 137.9, 135.8, 135.3, 135.1, 132.4, 131.2, 130.0, 127.9, 126.8, 126.4, 126.3, 126.2, 125.8, 125.2, 121.3, 117.0, 55.1, 54.5, 40.5, 39.2, 37.4, 26.1, 24.5, 19.0; HRMS (FAB^+) calcd for $C_{29}H_{32}N_7O_3$ (MH^+) m/z

526.2593, found 526.2582. Anal. calcd for $C_{29}H_{31}N_7O_3.0.5H_2O$: C, 65.2; H, 6.0; N, 18.3; found: C, 65.0; H, 5.8; N, 18.1%.

Example R.

***N*-{3-[{3-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}(methyl)amino]-propyl}-9-methyl-4-phenazinecarboxamide (45).** A solution of 9-methylphenazine-4-carboxylic acid (130 mg, 0.53 mmol) and CDI (100 mg, 0.61 mmol) in DMF (5 mL) was stirred at 55 °C for 6 h. The solution was cooled to 20 °C, diluted with dry benzene (10 mL), Sephadex LH-20 (300 mg) was added and the mixture stirred at 20 °C for 1 h. The mixture was filtered and the solvent evaporated. The residue was dissolved in dry THF (5 mL) and a solution of **40** (80 mg, 0.26 mmol) in THF (5 mL) added, and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–2%) of aqueous NH_3/(0-8%) MeOH/DCM, to give compound **45** (130 mg, 90%) as a red powder, mp (DCM/pet. ether) 138–142 °C; ^{1}H NMR δ 11.23 (br s, 1 H, CONH), 8.84 (d, J = 6.6 Hz, 1 H, ArH), 8.29 (d, J = 7.6 Hz, 1 H, ArH), 8.07 (d, J = 8.5 Hz, 1 H, ArH), 8.04 (d, J = 8.5 Hz, 1 H, ArH), 7.98 (d, J = 8.6 Hz, 1 H, ArH), 7.85 (t, J = 7.8 Hz, 1 H, ArH), 7.78-7.71 (m, 3 H, ArH, NH), 6.48 (t, J = 7.6 Hz, 1 H, ArH), 7.31 (t, J = 7.7 Hz, 1 H, ArH), 3.78–3.71 (m, 4 H, 2 × CH_2), 3.15 (br m, 4 H, 2 × CH_2), 2.88 (s, 3 H, CH_3), 2.73 (br s, 3 H, CH_3), 2.32, (br m, 2 H, CH_2), 2.21 (br m, 2 H, CH_2); ^{13}C NMR δ 165.6, 149.6, 143.2, 142.9, 140.7, 139.4, 137.9, 136.4, 135.4, 135.1, 133.7, 131.3, 131.2, 130.1, 129.7, 128.5, 127.7, 127.0, 121.3, 116.9, 54.9, 54.2, 40.2, 38.9, 37.3, 25.7, 24.3, 18.1. Anal. calcd for $C_{28}H_{30}N_8O_3$: C, 63.9; H, 5.9; N, 21.3; HRMS (FAB$^+$) calcd for ($C_{28}H_{31}N_8O_3$) (MH$^+$) m/z 527.2519 found 527.2533. Anal. calcd for $C_{28}H_{30}N_8O_3.1.75H_2O$: C, 60.3; H, 6.0; N, 20.1; found: C, 60.3; H, 5.6; N, 19.6%.

Example S.

***N*-{3-[(3-{[7-(2-Methoxyethoxy)-1,4-dioxido-1,2,4-benzotriazin-3-yl]amino}propyl)(methyl)amino]propyl}-4-acridinecarboxamide (55).**

3-Amino-1,2,4-benzotriazin-7-ol 1-oxide (46). A mixture of 4-amino-3-nitrophenol (5.0 g, 32.4 mmol) and cyanamide (8.2 g, 194.6 mmol) was heated at 100 °C for 10 min. The resulted solution was cooled to 20 °C and c.HCl (15 mL) was added dropwise, and the mixture was heated at 100 °C for 1.5 h, cooled to 20 °C. A solution

of 30% NaOH (40 mL) was then added and heated at 100 °C for 1 h. The reaction mixture was cooled to 20 °C, diluted with water (20 mL), and the precipitate was filtered, washed with water (100 mL), diethyl ether (100 mL), and dried to give amine 46 (5.45 g, 97%) as a yellow powder, mp > 300 °C [lit. (Friebe et. al. US Patent 5,856,325, *Jan* 5, 1999) mp (HOAc) >270 °C]; ^{1}H NMR [$(CD_3)_2SO$] δ 10.37 (br s, 1 H, OH), 7.48 (dd, *J* = 7.7, 2.6 Hz, 1 H, H-6), 7.40–7.37 (m, 2 H, H-5, H-8), 6.96 (br s, 2 H, NH_2).

7-(2-Methoxyethoxy)-1,2,4-benzotriazin-3-amine 1-oxide (47). A mixture of **46** (1.00 g, 5.8 mmol), dry K_2CO_3 (2.40 g, 17.4 mmol) and 2-bromoethyl methyl ether (2.42 g, 17.4 mmol) in DMF (20 mL) was heated at 80 °C for 2 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–3%) of MeOH/DCM, to give compound **47** (1.06 g, 77 %) as a yellow powder, mp (DCM/pet. ether) 201–203 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.07(d, *J* = 9.5 Hz, 1 H, H-5), 7.82 (br s, 2 H, NH_2), 7.76 (dd, *J* = 9.5, 2.6 Hz, 1 H, H-6), 7.50 (d, *J* = 2.6 Hz, 1 H, H-8), 4.26, (t, *J* = 4.3 Hz, 2 H, CH_2), 3.72 (t, *J* = 4.3 Hz, 2 H, CH_2), 3.33 (s, 3 H, OCH_3). Anal. calcd for $C_{10}H_{12}N_4O_5$: C, 50.8; H, 5.1; N, 23.7; found:C, 51.1; H, 5.0; N, 23.7%.

3-Hydroxy-7-(2-methoxyethoxy)-1,2,4-benzotriazine 1-oxide (48). A suspension of **47** (1.00 g, 4.2 mmol) in 2 N HCl (32 mL) was cooled to 5 °C and a solution of $NaNO_2$ (0.58 g, 8.5 mmol) in water (1.5 mL) was added over 1 h. More $NaNO_2$ (0.58 g, 8.5 mmol) in water (1.5 mL) was added and the suspension stirred 72 h at 20 °C. The precipitate was filtered and washed with water. The solid was dissolved in 5% aqueous NH_3 and filtered. The filtrate was acidified with conc. HCl to give a precipitate which was filtered dried and purified by chromatography, eluting with a gradient (0–5%) of MeOH/DCM to give compound **48** (0.68 g, 68 %) as a yellow solid, mp (DCM/pet.ether) 190–192 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.52 (br, 1 H, OH), 7.69 (br s, 1 H, H-8), 7.53 (dd, *J* = 8.8, 2.8 Hz, 1 H, H-6), 7.33 (d, *J* = 8.8 Hz, 1 H, H-5), 4.19 (t, *J* = 4.4 Hz, 2 H, CH_2), 3.68 (t, *J* = 4.4 Hz, 2 H, CH_2), 3.33 (s, 3 H, OCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 154.6, 152.9, 131.8, 129.5, 127.4, 117.8, 101.8, 70.0, 67.9, 58.1. Anal. calcd for $C_{10}H_{11}N_3O_4$: C, 50.6; H, 4.2; N, 17.7; found: C, 50.5; H, 4.7; N, 17.7.

3-Chloro-7-(2-methoxyethoxy)-1,2,4-benzotriazine 1-oxide (49). A mixture of **48** (1.00 g, 4.3 mmol) in $POCl_3$ (8 mL) was refluxed for 2 h. Excess reagent was evaporated under vacuum, and ice cold water (50 mL) was added to the residue, then solid Na_2CO_3 (1.0 g) was added portionwise. The resulting precipitate was filtered and purified by chromatography, eluting with a gradient (50–100 %) of DCM/pet. ether, to give compound **49** (0.90 g, 83%) as a pale yellow solid, mp (DCM/pet. ether) 121–125 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.00 (d, J = 9.2 Hz, 1 H, H-5), 7.81 (dd, J = 9.2, 2.9 Hz, 1 H, H-6), 7.68 (d, J = 2.8 Hz, 1 H, H-8), 4.35 (t, J = 4.4 Hz, 2 H, CH_2), 3.74 (t, J = 4.4 Hz, 2 H, CH_2), 3.33 (s, 3 H, OCH_3). Anal. calcd for $C_{10}H_{10}ClN_3O_3$: C, 47.0; H, 3.9; N,16.4, Cl, 13.9; found: C, 46.9; H, 4.3; N, 16.4; Cl, 13.7.

***N*^{1}-(3-Aminopropyl)-*N*^{3}-[7-(2-methoxyethoxy)-1-oxido-1,2,4-benzotriazin-3-yl]-*N*^{1}-methyl-1,3-propanediamine (51).** A solution of chloride **49** (0.90 g, 3.5 mmol) *tert*-butyl 3-[(3-aminopropyl)(methyl)amino]propylcarbamate (**50**) (1.60 g, 5.25 mmol) and Et_3N (4 ml) in DME (20 mL) was heated to 90 °C for 4 h. The solvent was evaporated, the residue was dissolved in MeOH (10 mL), and treated with methanolic HCl (100 mL). The reaction mixture was stirred at 20 °C for 20 h, the solvent evaporated and the residue partitioned between DCM and dil. aqueous NH_3. The aqueous layer was extracted with DCM (4 × 25 mL), the combined extracts dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–2%) of aqueous NH_3/(0–10%) MeOH/DCM, to give compound **51** (1.25 g, 98%) as a yellow solid, ^{1}H NMR [$(CD_3)_2SO$] δ 7.68 (br s, 1 H, NH), 7.55–7.52 (m, 1 H, ArH), 7.50-7.47 (m, 2 H, ArH), 4.20 (t, J = 4.4 Hz, 2 H, CH_2), 3.70 (t, J = 4.4 Hz, 2 H, CH_2), 3.34 (br m, 2 H, CH_2), 3.32 (s, 3 H, OCH_3), 2.54 (br t, J = 6.1 H, 2 H, CH_2), 2.35 (t, J = 6.9 Hz, 2 H, CH_2), 2.31 (t, J = 7.2 Hz, 2 H, CH_2), 2.13 (s, 3 H, NCH_3), 1.70 (br quin, J = 6.9 Hz, 2 H, CH_2), 1.47 (br quin, J = 7.0 Hz, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 158.3, 155.3, 144.5, 129.8, 138.3, 127.5, 98.9, 70.0, 67.7, 58.1, 55.0, 54.9, 41.8, 39.9, 39.1, 30.7, 26.2; HRMS (FAB$^+$) calcd for $C_{17}H_{29}N_6O_3$ (MH^+) m/z 365.2301, found 365.2311.

2,2,2-Trifluoro-*N*-{3-[(3-{[7-(2-methoxyethoxy)-1,4-dioxido-1,2,4-benzotriazin-3-yl]amino}propyl)(methyl)amino]propyl}acetamide (52). Ethyl trifluoroacetate (1.2 mL, 9.8 mmol) and H_2O (0.17 mL, 9.8 mmol) were added to a solution of **51** (1.19 g,

3.3 mmol) in CH_3CN and the reaction mixture was heated at reflux for 18 h. The solvent was evaporated and the residue partitioned between aqueous Na_2CO_3 solution and DCM. The aqueous layer was extracted with DCM, the combined organic extracts dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–5%) of MeOH/DCM to give compound **52** (1.3 g, 87%) as a yellow solid, mp (DCM/pet. ether) 117–119 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.43 (br s, 1 H, CONH), 7.66 (br t, J = 5.3 Hz, 1 H, NH), 7.54–7.45 (m, 3 H, ArH), 4.20 (t, J = 4.4 Hz, 2 H, CH_2), 3.70 (t, J = 4.4 Hz, 2 H, CH_2), 3.36–3.27 (m, 2 H, CH_2), 3.30 (s, 3 H, OCH_3), 3.21 (t, J = 7.0 Hz, 2 H, CH_2), 2.37 (t, J = 6.9 Hz, 2 H, CH_2), 2.31 (t, J = 6.9 Hz, 2 H, CH_2), 2.14 (s, 3 H, NCH_3), 1.70 (br quin, J = 7.0 Hz, 2 H, CH_2), 1.63 (br quin, J = 7.0 Hz, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 158.3, 156.5 (q, J = 18 Hz), 155.3,144.5, 129.8, 128.3, 127.5, 115.9 (q, J = 288 Hz), 98.9, 70.0, 67.7, 58.1, 54.8, 54.5, 41.5, 39.0, 37.7, 26.2, 25.8; HRMS (EI$^+$) calcd for $C_{19}H_{27}F_3N_6O_4$ (M^+) m/z 460.2046, found 460.2040. Anal. calcd for $C_{19}H_{27}F_3N_6O_4$ C, 49.6; H, 5.9; N, 18.3; F, 12.4; found:C, 49.9; H, 5.9; N, 18.2; F, 12.4%.

2,2,2-Trifluoro-*N*-{3-[(3-{[7-(2-methoxyethoxy)-1,4-dioxido-1,2,4-benzotriazin-3-yl]amino}propyl)(methyl)amino]propyl}acetamide (53). 70% H_2O_2 (1.05 mL, 21.7 mmol) was added dropwise to a solution of trifluoroacetic anhydride (3.0 mL, 21.7 mmol) in DCM (10 mL) at 5 °C. The solution was stirred at 5 °C for 10 min, 20 °C for 10 min, and then cooled to 5 °C. The solution was added dropwise to a solution of 1-oxide **52** (1.0 g, 2.2 mmol) and TFA (0.33 mL, 4.3 mmol) in DCM (50 mL). The reaction mixture was stirred at 20 °C for 18 h. The solution was partitioned between aqueous $NaHCO_3$ solution and DCM, the aqueous layer extracted further with DCM (5 × 30 mL), the combined extracts dried, and the solvent evaporated. The residue was chromatograped, eluting with a gradient (0–5%) of MeOH/DCM to give compound **53** (0.32 g, 30%) as a red solid, mp (DCM/pet. ether) 91–94 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.43 (br s, 1 H, CONH), 8.24 (t, J = 5.6 Hz, 1 H, NH,), 8.05 (d, J = 9.5 Hz, 1 H, H-5), 7.60 (dd, J = 9.5, 2.7 Hz, 1 H, H-6), 7.50 (d, J = 2.6 Hz, 1 H, H-8), 4.26 (t, J = 4.3 Hz, 2 H, CH_2), 3.72 (t, J = 4.3 Hz, 2 H, CH_2), 3.41 (br q, J = 6.6 Hz, 2 H, CH_2), 3.33 (s, 3 H, OCH_3), 3.23 (br q, J = 6.3 Hz, 2 H, CH_2), 2.38 (t, J = 6.7 Hz, 2 H, CH_2), 2.32 (t, J = 6.9 Hz, 2 H, CH_2), 2.15 (s, 3 H, NCH_3), 1.75 (br quin, J = 6.7 Hz, 2 H, CH_2), 1.65 (br quin, J = 6.9 Hz, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 157.0, 156.0 (q, J = 6

Hz), 149.0, 134.2, 130.2, 128.2, 120.2, 115.9 (q, $J = 279$ Hz), 99.5, 69.9, 68.0, 58.1, 54.9, 54.6, 41.5, 39.5, 37.7, 25.9, 25.8; HRMS (FAB$^+$) calcd for $C_{19}H_{28}F_3N_6O_5$ (MH$^+$) *m/z* 477.2073, found 477.2074.

***N*-{3-[(3-{[7-(2-Methoxyethoxy)-1,4-dioxido-1,2,4-benzotriazin-3-yl]amino}propyl)(methyl)amino]propyl}-4-acridinecarboxamide (55).** A solution of trifluoroacetamide **53** (1.55 g, 0.33 mmol) and aqueous NH_3 (8 mL) in MeOH (10 mL) was stirred at 20 °C for 18 h. The solvent was evaporated and the residue dried to give the intermediate amine **54** as a red solid. The solid was dissolved in dry THF (10 mL) and 4-(1*H*-imidazol-1-ylcarbonyl)acridine (0.18 g, 0.65 mmol) added and solution stirred at 20 °C for 72 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–2 %) of aqueous NH_3/(0–5 %)MeOH/DCM, to give compound **55** (150 mg, 79%) as a red solid, mp (DCM/pet. ether) 98–103 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.32 (t, $J = 5.3$ Hz, 1 H, CONH), 9.27 (s, 1 H, NH), 8.68 (dd, $J = 7.0$, 1.5 Hz, 1 H, ArH), 8.33 (dd, $J = 8.4$, 1.3 Hz, 1 H, ArH), 8.27–8.18 (m, 3 H, ArH), 7.96–7.91 (m, 2 H, ArH), 7.72 (dd, $J = 8.2$, 7.2 Hz, 1 H, ArH), 7.66 (t, $J = 7.3$ Hz, 1 H, ArH), 7.50 (dd, $J = 9.5$, 2.6 Hz, 1 H, ArH), 7.40 (d, $J = 2.6$ Hz, 1 H, ArH), 4.23 (t, $J = 4.3$ Hz, 2 H, CH_2), 3.71 (t, $J = 4.4$ Hz, 2 H, CH_2), 3.59 (br q, $J = 6.4$ Hz, 2 H, CH_2), 3.43 (br q, $J = 6.4$ Hz, 2 H, CH_2), 2.56 (t, $J = 7.0$ Hz, 2 H, CH_2), 2.46 (t, $J = 6.7$ Hz, 2 H, CH_2), 2.23 (s, 3 H, NCH_3), 1.91 (br quin, $J = 6.8$ Hz, 2 H, CH_2), 1.78 (br quin, $J = 6.6$ Hz, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 164.6, 156.9, 148.9, 146.9, 145.4, 138.5, 134.3, 134.1, 132.6, 131.8, 130.0, 128.5, 128.3, 128.3, 128.0, 126.4, 126.3, 125.5, 125.1, 118.4, 99.4, 69.9, 68.0, 58.1, 55.2, 55.0, 41.8, 39.7, 37.4, 26.9, 25.8; HRMS (FAB$^+$) calcd for $C_{31}H_{36}N_7O_5$ (MH$^+$) *m/z* 586.2778, found 586.2768. Anal. calcd for $C_{31}H_{35}N_7O_5$: C, 63.6; H, 6.0; N, 16.7; found:C, 62.3; H, 6.1; N, 16.5%.

Example T.

***N*-{2-[[3-(1,4-Dioxido-1,2,4-benzotriazin-3-yl)propyl](methyl)amino]propyl}-4-acridinecarboxamide (62).**

3-Allyl-1,2,4-benzotriazine 1-oxide (56). $Pd(PPh_3)_4$ (640 mg, 0.55 mmol) was added to a stirred solution of chloride **3** (2.0 g, 11.0 mmol) and allyltributyltin (3.8 mL, 12.1 mmol), the solution degassed, and stirred under N_2 at reflux temperature for 6 h. The

solvent was evaporated and the residue purified by chromatography, eluting with 20% EtOAc/pet. ether to give an oil which was purified by chromatography, eluting with 5% EtOAc/DCM, to give alkene **56** (1.92 g, 93%) as a white solid, mp (EtOAc/pet. ether) 57–58 °C, ^{1}H NMR δ 8.45 (dd, J = 8.6, 1.4 Hz, 1 H, H-8), 8.10 (dd, J = 8.4, 1.4 Hz, 1 H, H-5), 7.94 (ddd, J = 8.4, 7.1, 1.4 Hz, 1 H, H-6), 7.70 (ddd, J = 8.6, 7.1, 1.4 Hz, 1 H, H-7), 6.15-6.24 (m, 1 H, H-2'), 5.31 (dq, J = 17.0, 1.5 Hz, 1 H, H-3'), 5.24 (dq, J = 10.1, 1.5 Hz, 1 H, H-3'), 3.80 (dq, J = 6.8, 1.5 Hz, 2 H, H-1'); ^{13}C NMR δ 165.2, 147.5, 135.6, 133.3, 132.7, 130.1, 128.8, 120.8, 118.5, 41.8. Anal. calcd for $C_{10}H_9N_3O$: C, 64.2; H, 4.85; N, 22.45; found:C, 63.85; H, 4.9; N, 22.7%.

3-(3-Hydroxypropyl)-1,2,4-benzotriazine 1-oxide (57). A solution of 9-BBN in THF (13.7 mL, 6.8 mmol) was added to a stirred solution of alkene **56** (1.07 g, 5.7 mmol) in THF (50 mL) and the solution stirred at 20 °C for 1 h. A solution of NaOH (3 M; 2.9 ml, 8.5 mmol), followed by 35% H_2O_2 (2.6 mL, 25.6 mmol) were carefully added and the mixture stirred at 20 °C for 1 h. The mixture was diluted with brine (100 mL), extracted with EtOAc (3 × 100 mL), the combined organic fraction dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (10–50%) of EtOAc/DCM, to give alcohol **57** (1.02 g, 87%) as a white solid, mp (EtOAc/pet. ether) 99–100 °C; ^{1}H NMR δ 8.46 (dd, J = 8.7, 1.0 Hz, 1 H, H-8), 7.99 (dd, J = 8.5, 1.2 Hz, 1 H, H-5), 7.93 (ddd, J = 8.5, 7.0, 1.0 Hz, 1 H, H-6), 7.70 (ddd, J = 8.7, 7.0, 1.2 Hz, 1 H, H-7), 3.80 (t, J = 6.1 Hz, 2 H, CH_2O), 3.18 (t, J = 7.3 Hz, 2 H, CH_2), 2.15–2.22 (m, 2 H, CH_2), (OH not observed); ^{13}C NMR δ 166.9, 147.3, 135.7, 133.3, 130.1, 128.6, 120.1, 62.1, 34.1, 30.5. Anal. calcd for $C_{10}H_{11}N_3O_2$: C, 58.5; H, 5.4 ;N, 20.5; found:C, 58.6; H, 5.5; N, 20.5%.

***tert*-Butyl 3-{methyl[3-(1-oxido-1,2,4-benzotriazin-3-yl)propyl]amino}propylcarbamate (58).** MsCl (0.52 mL, 6.7 mmol) was added dropwise to a stirred solution of alcohol 57 (1.06 g, 5.2 mmol) and Et_3N (1.1 mL, 7.8 mmol) in DCM (50 mL) and the solution stirred at 20 °C for 1 h. The solution was diluted with DCM (50 mL), washed with water (2 × 30 mL), dried, and the solvent evaporated. The residue was dissolved in dry DMF (20 mL) and *tert*-butyl 3-(methylamino)propylcarbamate (Rennard et al. *Org. Lett.*, **2000**, *2*, 2117-2120) (9.7 g, 51.6 mmol) added and the solution stirred at 50 °C for 3 h. The solvent was

evaporated and the residue partitioned between EtOAc (100 mL) and aqueous $KHCO_3$ solution (100 mL). The organic fraction was washed with water (2 × 50 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–10%) of MeOH/DCM, to give compound **58** (0.93 g, 48%) as a pale yellow oil, ^{1}H NMR δ 8.45 (dd, J = 8.9, 1.4 Hz, 1 H, H-8), 8.10 (br d, J = 8.3 Hz, 1 H, H-5), 7.93 (ddd, J = 8.3, 7.0, 1.4 Hz, 1 H, H-6), 7.70 (ddd, J = 8.9, 7.0, 1.5 Hz, 1 H, H-7), 5.38 (br s, 1 H, NH), 3.17–3.22 (m, 2 H, CH_2N), 3.07 (dd, J = 7.7, 7.4 Hz, 2 H, CH_2), 2.55–2.60 (m, 2 H, CH_2N), 2.49–2.53 (m, 2 H, CH_2N), 2.28 (s, 3 H, NCH_3), 2.10-2.18 (m, 2 H, CH_2), 1.68-1.73 (m, 2 H, CH_2), 1.42 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR δ 166.7, 156.1, 147.5, 135.6, 133.3, 130.0, 128.7, 120.1, 78.9, 56.7, 55.6, 41.5, 39.3, 34.9, 28.3 (3), 26.6, 25.0; MS (FAB$^+$) m/z 376 (MH$^+$, 55%), 360 (5); HRMS (FAB$^+$) calcd for $C_{19}H_{30}N_5O_3$ (MH$^+$) m/z 376.2349, found 376.2345.

2,2,2-Trifluoro-*N*-(3-{methyl[3-(1-oxido-1,2,4-benzotriazin-3-yl)propyl]amino}propyl)acetamide (59). A solution of carbamate 58 (0.51 g, 1.35 mmol) in HCl saturated MeOH (30 mL) was stirred at 50 °C for 3 h. The solvent was evaporated and the residue partitioned between dil. aqueous NH_3 (50 ml) and $CHCl_3$ (50 mL). The aqueous fraction was extracted with $CHCl_3$ (3 × 30 mL), the combined organic fraction dried, and the solvent evaporated. The residue was dissolved in MeCN (30 mL) and ethyl trifluoroacetate (0.24 mL, 2.03 mmol) and water (30 µL, 1.5 mmol) added. The solution was stirred at reflux temperature for 16 h, cooled to 20 °C and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–10%) of MeOH/DCM, to give amide **59** (460 mg, 92%) as a pale yellow oil, ^{1}H NMR [$(CD_3)_2SO$] δ 9.41 (br s, 1 H, CONH), 8.37 (d, J = 8.6 Hz, 1 H, H-8), 8.07 (ddd, J = 8.3, 6.9, 1.4 Hz, 1 H, H-6), 8.02 (dd, J = 8.3, 1.3 Hz, 1 H, H-5), 7.83 (ddd, J = 8.6, 6.9, 1.3 Hz, 1 H, H-7), 3.17–3.22 (m, 2 H, CH_2N), 2.95 (dd, J = 7.6, 7.4 Hz, 2 H, CH_2), 2.42 (br t, J = 6.8 Hz, 2 H, CH_2N), 2.33 (br t, J = 6.7 Hz, 2 H, CH_2N), 2.16 (s, 3 H, NCH_3), 1.92–2.00 (m, 2 H, CH_2), 1.57–1.64 (m, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 166.2, 156.0 (q, J = 37 Hz), 146.9, 136.0, 132.8, 130.4, 128.3, 119.5, 115.9 (q, J = 288 Hz), 56.1, 54.4, 41.4, 37.6, 34.2, 25.7, 24.8; MS (EI$^+$) m/z 371 (M$^+$, 7%), 354 (100); HRMS (EI$^+$) calcd for $C_{16}H_{20}F_3N_5O_2$ (M$^+$) m/z 371.1569, found 371.1560.

***N*-{3-[[3-(1,4-Dioxido-1,2,4-benzotriazin-3-yl)propyl](methyl)amino]propyl}-2,2,2-trifluoroacetamide (60).** H_2O_2 (0.6 mL, 12.2 mmol) was added dropwise to a stirred solution of trifluoroacetic anhydride (1.7 mL, 12.2 mmol) in DCM (10 mL) at 5 °C. The mixture was stirred at 5 °C for 5 min., warmed to 20 °C for 20 min., cooled to 5 °C, and added to a stirred solution of amide **59** (453 mg, 1.2 mmol) and trifluoroacetic acid (0.19 mL, 2.4 mmol) in $CHCl_3$ (10 mL) at 5 °C. The mixture was stirred at 20 °C for 4 h, diluted with aqueous $KHCO_3$ (15 mL), and extracted with $CHCl_3$ (5 × 30 mL). The combined organic fraction was dried, adsorbed on to silica, and the solvent evaporated (CAUTION: use blast shield). The residue was purified by chromatography, eluting with a gradient (0–10%) of MeOH/DCM, to give 1,4-dioxide **60** (268 mg, 57%) as a yellow oil, ^{1}H NMR [$(CD_3)_2SO$] δ 9.40 (br s, 1 H, NHCO), 8.34–8.38 (m, 2 H, H-5, H-8), 8.10 (ddd, J = 8.7, 7.1, 1.2 Hz, 1 H, H-6), 7.94 (ddd, J = 8.5, 7.1, 1.3 Hz, 1 H, H-7), 3.16–3.21 (m, 2 H, CH_2N), 3.04 (dd, J = 7.6, 7.4 Hz, 2 H, CH_2), 2.43 (br t, 6.8 Hz, 2 H, CH_2N), 2.32 (br t, J = 6.8 Hz, 2 H, CH_2), 2.14 (s, 3 H, NCH_3), 1.87–1.94 (m, 2 H, CH_2), 155-1.62 (m, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 155.9 (q, J = 37 Hz), 154.7, 139.3, 135.4, 134.4, 131.7, 120.9, 118.8, 115.8 (q, J = 288 Hz), 56.2, 54.3, 41.3, 37.6, 27.6, 25.8, 21.8; MS (FAB$^+$) m/z 388 (MH$^+$, 25%), 372 (5); HRMS (FAB$^+$) calcd for $C_{16}H_{21}F_3N_5O_3$ (MH$^+$) m/z 388.1597, found 388.1601.

***N*^{1}-[3-(1,4-Dioxido-1,2,4-benzotriazin-3-yl)propyl]-*N*^{1}-methyl-1,3-propanediamine (61).** Aq. ammonia (5 mL) was added to a stirred solution of amide **60** (169 mg, 0.44 mmol) in MeOH (10 mL) and the solution stirred at 40 °C for 6 h. The solvent was evaporated to give crude amine **61** as a brown oil, ^{1}H NMR [$(CD_3)_2SO$] δ 8.34–8.39 (m, 2 H, H-5, H-8), 8.14 (ddd, J = 8.6, 7.0, 1.1 Hz, 1 H, H-6), 7.96 (ddd, J = 8.5, 7.0, 1.2 Hz, 1 H, H-7), 7.61 (br s, 2 H, NH_2), 3.04 (dd, J = 7.6, 7.4 Hz, 2 H, CH_2N), 2.85 (br dd, J = 7.4, 7.2 Hz, 2 H, CH_2), 2.45 (br t, J = 6.9 Hz, 2 H, CH_2N), 2.39 (br t, J = 6.7 Hz, 2 H, CH_2N), 2.17 (s, 3 H, NCH_3), 1.88–1.95 (m, 2 H, CH_2), 1.63–170 (m, 2 H, CH_2).

***N*-{3-[[3-(1,4-dioxido-1,2,4-benzotriazin-3-yl)propyl](methyl)amino]propyl}-4-acridinecarboxamide (62).** The crude amine **61** was dissolved in dry THF (10 mL) and 4-(1*H*-imidazol-1-ylcarbonyl)acridine (0.18 g, 0.65 mmol) added and solution

stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–10 %) of MeOH/DCM, to give compound **62** (86 mg, 40%) as a yellow gum, which was converted to the hydrochloride salt, a pale green gum, ^{1}H NMR [$(CD_3)_2SO$] δ 11.29 (br s, 1 H, CONH), 10.90 (br s, 1 H, NH^+Cl^-), 9.38 (s, 1 H, H-9), 8.74 (dd, J = 7.0, 1.0 Hz, 1 H, H-3), 8.47 (d, J = 8.7 Hz, 1 H, H-1), 8.42 (dd, J = 8.4, 1.2 Hz, 1 H, H-5), 8.35 (dd, J = 8.6, 0.7 Hz, 1 H, H-8'), 8.31 (d, J = 8.7 Hz, 1 H, H-8), 8.21 (d, J = 8.4 Hz, 1 H, H-5'), 8.11 (ddd, J = 8.7, 7.0, 1.3 Hz, 1 H, H-6), 7.94–8.10 (m, 2 H, H-2, H-6'), 7.78 (dd, J = 8.7, 7.0 Hz, 1 H, H-7), 7.67–7.71 (m, 1 H, H-7'), 3.65–3.70 (m, 2 H, CH_2N), 3.30–3.37 (m, 2 H, CH_2N), 3.19–3.28 (m, 2 H, CH_2N), 3.09 (t, J = 7.3 Hz, 2 H, CH_2), 2.79 (d, J = 4.8 Hz, 3 H, NCH_3), 2.16–2.27 (m, 4 H, 2 × CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 165.3, 153.0, 146.3, 144.7, 139.6, 139.2, 135.5, 134.7, 134.5, 134.0, 133.0, 132.3, 132.0, 128.4, 128.1, 126.6, 126.3, 125.5, 125.3, 120.9, 118.8, 53.7, 52.7, 39.4, 36.4, 26.8, 23.7, 18.8; MS (FAB$^+$) m/z 497 (MH$^+$, 12%), 481 (3); HRMS (FAB$^+$) calcd for $C_{28}H_{29}N_6O_3$ (MH$^+$) m/z 497.2301, found 497.2301.

Example U.

***N*-{3-[[3-(1,4-Dioxido-1,2,4-benzotriazin-3-yl)propyl](methyl)amino]propyl}-1-phenazinecarboxamide (63).** Aq. ammonia (5 mL) was added to a stirred solution of amide **60** (61 mg, 0.16 mmol) in MeOH (10 mL) and the solution stirred at 40 °C for 6 h. The solvent was evaporated to give crude amine **61** as a brown oil.

The crude amine 61 was dissolved in dry THF (10 mL) and 1-(1*H*-imidazol-1-ylcarbonyl)phenazine (100 mg, 0.36 mmol) added and solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–10%) of MeOH/DCM, to give compound **63** (44 mg, 56%) as a yellow gum, which was converted to the hydrochloride salt and recrystallised, mp (MeOH/EtOAc) 173 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 10.31 (t, J = 5.8 Hz, 1 H, NH), 9.90 (br s, 1 H, NH^+Cl^-), 8.61 (dd, J = 7.1, 1.4 Hz, 1 H, H-2), 8.48 (dd, J = 9.1, 1.4 Hz, 1 H, H-9), 8.42 (dd, J = 8.6, 1.4 Hz, 1 H, H-4), 8.34 (d, J = 8.4 Hz, 1 H, H-6), 8.30 (dd, J = 8.6, 1.1 Hz, 1 H, H-8'), 8.26 (dd, J = 8.3, 1.4 Hz, 1 H, H-5'), 7.93–8.13 (m, 5 H, H-3, H-7, H-8, H-6', H-7'), 3.62–3.67 (m, 2 H, CH_2N), 3.30–3.34 (m, 2 H, CH_2N), 3.22–3.38 (m, 2 H, CH_2N), 3.07–3.11 (m, 2 H, CH_2), 2.82 (br s, 3 H, NCH_3), 2.10–2.22 (m, 4 H, 2 × CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 164.8, 153.1, 142.7, 142.5,

141.2, 140.0, 139.2, 135.6, 134.5, 133.5, 132.7, 132.0, 131.9, 131.6, 130.9, 130.3, 129.4, 129.1, 121.0, 118.8, 54.0, 52.9, 39.4, 36.4, 26.7, 23.8, 19.0; MS (FAB$^+$) *m/z* 498 (MH$^+$, 20%), 482 (5); HRMS (FAB$^+$) calcd for $C_{27}H_{28}N_7O_3$ (MH$^+$) *m/z* 498.2254, found 498.2256.

Example V

3-[(7-Chloro-4-quinolinyl)amino]-*N*-{3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}propanamide (65).

A solution of *N*-(7-chloro-4-quinolinyl)-β-alanine (**64**) (Titus et al, *J. Org. Chem.*, **1948,** *13*, 39-62) (303 mg, 1.2 mmol) and CDI (235 mg, 1.5 mmol) in DMF (5 mL) was stirred at 50 °C for 1 h. The solvent was evaporated and the residue crystallised from DCM/pet. ether to give the imidazolide (290 mg, 80%), which was used directly. A solution of N^1-(1,4-dioxido-1,2,4-benzotriazin-3-yl)-1,3-propanediamine (**16**) (92 mg, 390 μmol) and imidazolide (176 mg, 590 μmol) in DMF (10 mL) was stirred at 20 °C for 3 days, the solvent evaporated and the residue recrystallised from hot MeOH to give compound **65** (84 mg, 46%) as a red powder, mp (MeOH) 202 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 8.40 (d, J = 5.4 Hz, 1 H, H-2'), 8.26 (br t, J = 6.2 Hz, 1 H, NH), 8.18–8.12 (m, 2 H, H-5, H-8), 8.13 (d, J = 8.6 Hz, 1 H, H-5'), 7.99 (br t, J = 5.7 Hz, 1 H, NH), 7.93 (ddd, J = 8.6, 7.1, 1.2 Hz, 1 H, H-6), 7.75 (d, J = 2.2 Hz, 1 H, H-8'), 7.56 (ddd, J = 8.6, 7.1, 1.3 Hz, 1 H, H-7), 7.40 (dd, J = 8.6, 2.2 Hz, 1 H, H-6'), 7.37 (br t, J = 5.4 Hz, 1 H, NH), 6.52 (d, J = 5.4 Hz, 1 H, H-3'), 3.49–3.54 (m, 2 H, CH_2N), 3.36–3.41 (m, 2 H, CH_2N), 3.12–3.17 (m, 2 H, CH_2N), 2.47–2.51 (m, 2 H, CH_2), 1.70–1.77 (m, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 170.3, 151.8, 149.7, 149.6, 149.0, 138.1, 135.4, 133.2, 129.8, 127.4, 126.8, 124.0, 123.9, 121.0, 117.4, 116.8, 99.7, 39.0, 38.2, 35.8, 34.3, 28.5; MS (FAB$^+$) *m/z* 470 (MH$^+$, 5%), 468 (15), 454 (1), 452 (3): HRMS (FAB$^+$) calcd for $C_{22}H_{23}{}^{35}ClN_7O_3$ (MH$^+$) *m/z* 468.1551, found 468.1546; calcd for $C_{22}H_{23}{}^{37}ClN_7O_3$ (MH$^+$) *m/z* 470.1540, found 470.1535.

Example W.

***N*-[3-(Methyl{3-[(7-methyl-1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]-4-acridinecarboxamide (74).**

7-Methyl-1,2,4-benzotriazin-3-ol 1-Oxide (67). $NaNO_2$ (9.0g, 130.6 mmol) was added in small portions to a stirred solution of 7-methyl-1,2,4-benzotriazin-3-amine 1-

oxide [Hay et al, *J. Med. Chem.* **2003**, 46, 169–182] (**66**) (11.5 g, 65.3 mmol) in TFA (40 mL) at –5 to 0 °C. After the addition was completed stirring was continued for a further 1 h, the mixture was poured into ice (300 g) and stirred 1 h. The resulting pale yellow precipitate was filtered and washed with water. The precipitate was dissolved in 8% aqueous NH_3, filtered and the filtrate was acidified with cHCl. The resulting precipitate was filtered, washed with water and dried to give alcohol **67** (11.5 g, 100%) which was used without further purification.

3-Chloro-7-methyl-1,2,4-benzotriazine 1-Oxide (68). Alcohol **67** (3.15 g, 65.3 mmol) was refluxed in $POCl_3$ (50 mL) for 5 h. The reaction mixture was cooled and carefully poured into ice/water and stirred for 30 min. The resulting precipitate was filtered, air dried and purified by chromatography, eluting with a gradient (50–100%) of DCM/hexane, to give chloride **68** (9.0 g, 66%), mp (DCM/hexane) 174–176 °C; ^{1}H NMR δ 8.20 (br s, 1 H, H-8), 7.89 (d, J = 8.6 Hz, 1 H, H-5), 7.82 (dd, J = 8.6, 1.9 Hz, 1 H, H-6), 2.61 (s, 3 H, CH_3). Anal. calcd for $C_8H_6ClN_3O$: C, 49.1; H, 3.1; N, 21.5; Cl, 18.1, found:C, 49.1, H, 3.1; N, 21.5; Cl, 18.5%.

***tert*-Butyl 3-(Methyl-{3-[(7-methyl-1-oxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propylcarbamate (70).** A mixture of chloride **68** (2.18 g, 11.1 mmol), *tert*-butyl 3-[(3-aminopropyl)(methyl)amino]propylcarbamate **69** (4.35 g, 17.8 mmol) and Et_3N (2.3 mL, 16.5 mmol) in DME (25 mL) was heated at 85 °C for 3 h. The solvent was evaporated, the residue was dissolved in DCM (100 mL) and washed with aqueous NH_3. The organic layer was separated and the aqueous layer further extracted with DCM (3 × 30 mL). The combined organic fraction was dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(0–5%) MeOH/DCM, to give **70** (3.7 g, 93%) as a yellow solid, mp (DCM/hexane) 117–120 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.94 (s, 1 H, H-8), 7.79 (br s, 1 H, NH), 7.62 (dd, J = 8.7, 2.0 Hz, 1 H, H-6), 7.49 (d, J = 8.6 Hz, 1 H, H-5), 6.75 (t, J = 5.3 Hz, 1 H, NH), 3.34 (br q, J = 6.4 Hz, 2 H, CH_2), 2.93 (br q, J = 6.5 Hz, 2 H, CH_2), 2.41 (s, 3 H, CH_3), 2.35 (t, J = 6.9 Hz, 2 H, CH_2), 2.27 (t, J = 7.0 Hz, 2 H, CH_2), 2.12 (s, 3 H, CH_3), 1.70 (br quin, J = 6.9 Hz, 2 H, CH_2), 1.51 (br quin, J = 7.1 Hz, 2 H, CH_2), 1.35 (s, 9 H, 3 × CH_3); ^{13}C NMR [$(CD_3)_2SO$] 158.6, 155.4,

146.8, 137.5, 134.4, 129.5, 125.7, 118.4, 77.2, 54.8, 54.7, 41.6, 39.0, 38.2, 28.1 (3), 27.1, 26.1, 20.6.

N^1-(3-Aminopropyl)-N^1-methyl-N^3-(6-methyl-1-oxido-1,2,4-benzotriazin-3-yl)-1,3-propanediamine (71). Carbamate **70** (4.1 g, 10.1 mmol) was dissolved in methanolic HCl (50 mL) and stirred for 48 h at 20 °C. Excess reagent and solvent were evaporated and the residue was partitioned between DCM and aqueous NH_3, the organic layer was separated and the aqueous layer was further extracted with DCM (4 × 30 mL). The combined organic fraction was dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(3–10%) MeOH/DCM, to give amine **71** (1.14 g, 100%) as a yellow solid, ^{1}H NMR [$(CD_3)_2SO$] δ 7.94 (s, 1 H, H-8), 7.81 (br s, 1 H, NH), 7.63 (dd, J = 8.7, 1.9 Hz, 1 H, H-6), 7.49 (d, J = 8.6 Hz, 1 H, H-5), 3.34 (br q, J = 6.3 Hz, 2 H, CH_2), 2.54–2.58 (m, 2 H, CH_2), 2.41 (s, 3 H, CH_3), 2.36 (t, J = 6.9 Hz, 2 H, CH_2), 2.31 (t, J = 7.2 Hz, 2 H, CH_2), 2.13 (s, 3 H, CH_3), 1.71 (br quin, J = 7.0 Hz, 2 H, CH_2), 1.48 (br quin, J = 7.0 Hz, 2 H, CH_2), NH_2 not observed; HRMS (FAB$^+$) calcd for $C_{15}H_{25}N_6O$ (MH$^+$) m/z 305.2090, found 305.2090.

2,2,2-Trifluoro-N-[3-(methyl-{3-[(7-methyl-1-oxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]acetamide (72). CF_3CO_2Et (2.43 mL, 20.4 mmol) and H_2O (0.36 mL, 20.4 mmol) were added to a solution of amine **71** (3.1 g, 10.2 mmol) in CH_3CN (50 mL) and the reaction mixture heated at reflux for 20 h. The solvent was evaporated and residue partitioned between DCM and aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was further extracted with DCM (3 × 50 mL). The combined organic fraction was dried and the solvent evaporated to give acetamide **72** (3.75 g, 92%) as a yellow solid, mp (DCM/hexane) 121–124 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.44 (br s, 1 H, NH), 7.94 (s, 1 H, H-8), 7.80 (br s, 1 H, NH), 7.62 (dd, J = 8.7, 1.9 Hz, 1 H, H-6), 7.48 (d, J = 8.6 Hz, 1 H, H-5), 3.22 (br q, J = 6.5 Hz, 2 H, CH_2), 2.41 (s, 3 H, CH_3), 2.37 (t, J = 7.0 Hz, 2 H, CH_2), 2.32 (t, J = 6.9 Hz, 2 H, CH_2), 2.15 (s, 3 H, CH_3), 1.71 (br quin, J = 7.0 Hz, 2 H, CH_2), 1.63 (br quin, J = 6.5 Hz, 2 H, CH_2), CH_2 not observed; ^{13}C NMR [$(CD_3)_2SO$] δ 158.6, 156.3 (q, J= 36 Hz), 146.8, 137.6, 134.5, 129.6, 125.7, 118.4, 116.1 (q, J = 288 Hz), 54.7, 54.5, 41.5, 39.0, 37.8, 26.1, 25.8, 20.6; HRMS (FAB$^+$) calcd for $C_{17}H_{24}F_3N_6O_2$

(MH$^+$) *m/z* 401.1913, found 401.1896. Anal. calcd for $C_{17}H_{23}F_3N_6O_2$: C, 51.0; H, 5.8; F, 14.2; N, 21.0; found:C, 51.3; H, 5.9; F, 14.0; 21.0%.

2,2,2-Trifluoro-*N*-[3-(methyl{3-[(7-methyl-1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]acetamide (73). A solution of trifluoroperacetic acid [made from trifluoroacetic anhydride (12.4 mL, 89.4 mmol) and 70% H_2O_2 (4.3 mL, 89.4 mmol) in DCM (50 mL)] was added to a solution of acetamide **72** (3.6 g, 8.9 mmol) and trifluoroacetic acid (2.8 mL, 35.8 mol) in DCM (50 mL) at 0 °C and the reaction mixture was stirred at 20 °C for 18 h. The reaction mixture was slowly added to a solution of aqueous $NaHCO_3$ (100 mL) at 5 °C. The organic layer was separated and the aqueous layer was further extracted with DCM (4 × 30 mL). The combined organic fraction was dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–8%) of MeOH/DCM, to give (i) starting material (1.44 g, 40%) and (ii) acetamide **73** (1.30 g, 35%) as a red solid, mp (DCM/hexane) 117–119 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.44 (br s, 1 H, NH), 8.36 (t, J = 5.9 Hz, 1 H, NH), 8.03 (d, J = 8.9 Hz, 1 H, H-5), 8.01 (s, 1 H, H-8), 7.78 (dd, J = 8.9, 1.6 Hz, 1 H, H-6), 3.42 (br q, J = 6.6 Hz, 2 H, CH_2), 3.23 (br q, J = 6.5 Hz, 2 H, CH_2), 2.47 (s, 3 H, CH_3), 2.38 (t, J = 6.7 Hz, 2 H, CH_2), 2.32 (t, J = 6.9 Hz, 2 H, CH_2), 2.15 (s, 3 H, CH_3), 1.75 (br quin, J = 6.9 Hz, 2 H, CH_2), 1.65 (br quin, J = 7.1 Hz, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 156.0 (q, J = 36 Hz), 149.4, 137.4, 137.2, 136.7, 129.6, 119.4, 116.6, 115.9 (q, J = 288 Hz), 54.9, 54.6, 41.5, 39.5, 37.6, 26.0, 25.8, 20.7; HRMS (FAB$^+$) calcd for $C_{17}H_{24}F_3N_6O_3$ (MH$^+$) *m/z* 417.1862, found 417.1859. Anal. calcd for $C_{17}H_{23}F_3N_6O_3$: C, 49.0; H, 5.6; F, 13.7; N, 20.2; found:C, 49.3; H, 5.5; F, 13.6; N, 20.2%.

***N*-[3-(Methyl{3-[(7-methyl-1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]-4-acridinecarboxamide (74).** Aqueous NH_3 (5 mL) was added to a solution of acetamide **73** (135 mg, 0.32 mmol) in MeOH (10 mL) and the reaction mixture stirred at 20 °C for 18 h. The solvent was evaporated, the residue was dissolved in DMF (5 mL), 4-(1*H*-imidazol-1-ylcarbonyl)acridine (177 mg, 0.64 mmol) was added and the mixture stirred at 20 °C for 48 h. The solvent was evaporated and the residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(0–5%) MeOH/DCM, to give compound **74** (168 mg, 100%)

as a red solid, mp (DCM/hexane) 166–168 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.32 (br s, 1 H, NH), 9.26 (s, 1 H, ArH), 8.68 (d, J = 6.7 Hz, 1 H, ArH), 8.37 (t, J = 5.6 Hz, 1 H, NH), 8.33 (d, J = 8.0 Hz, 1 H, ArH), 8.23 (d, J = 8.7 Hz, 1 H, ArH), 8.17 (d, J = 8.4 Hz, 1 H, ArH), 7.89–7.96 (m, 3 H, ArH), 7.64–7.74 (m, 3 H, ArH), 3.59 (br q, J = 6.0 Hz, 2 H, CH_2), 3.41 (br q, J = 6.2 Hz, 2 H, CH_2), 2.56 (t, J = 7.0 Hz, 2 H, CH_2), 2.46 (t, J = 6.9 Hz, 2 H, CH_2), 2.44 (s, 3 H, CH_3), 2.23 (s, 3 H, CH_3), 1.91 (br quin, J = 6.7 Hz, 2 H, CH_2), 1.79 (br quin, J = 6.6 Hz, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 164.7, 149.2, 147.0, 145.4, 138.5, 137.2, 137.1, 136.5, 134.3, 132.6, 131.8, 129.4, 128.5, 128.4, 128.3, 126.4, 126.4, 125.5, 125.2, 119.3, 116.5, 55.3, 55.1, 41.8, 39.5, 37.4, 26.9, 25.9, 20.7; HRMS (FAB$^+$) calcd for $C_{29}H_{32}N_7O_3$ (MH$^+$) m/z 526.2567, found 526.2537. Anal. calcd for $C_{29}H_{31}N_7O_3 \cdot \frac{1}{4}H_2O$: C, 65.7; H, 6.0; N, 18.5; found:C, 65.8; H, 5.9; N, 18.7%.

Example X

***N*-[3-(Methyl{3-[(7-methyl-1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]-2-(4-pyridinyl)-8-quinolinecarboxamide (75).** Aqueous NH_3 (5 mL) was added to a solution of acetamide **73** (135 mg, 0.32 mmol) in MeOH (5 mL) and the mixture stirred at 20 °C for 18 h. The solvent was evaporated, the residue dissolved in DMF (5 mL) and 8-(1*H*-imidazol-1-ylcarbonyl)-2-(4-pyridinyl)quinoline (160 mg, 0.64 mmol) was added and the mixture stirred at 20 °C for 48 h. The solvent was evaporated, the residue dissolved in DCM (20 mL) and washed with water (3 × 15 mL). The organic layer was separated, dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(0–3%) MeOH/DCM, to give compound **75** (158 mg, 89%) as a red solid, mp (DCM/hexane) 178–180 °C; ^{1}H NMR δ 10.89 (t, J = 4.9 Hz, 1 H, NH), 8.80–8.84 (m, 3 H, ArH), 8.36 (d, J = 8.6 Hz, 1 H, ArH), 8.28 (t, J = 4.8 Hz, 1 H, NH), 8.05 (s, 1 H, ArH), 8.02 (d, J = 8.9 Hz, 1 H, ArH), 7.90–7.95 (m, 4 H, ArH), 7.67 (t, J = 7.7 Hz, 1 H, ArH), 7.56 (dd, J = 8.9, 1.7 Hz, 1 H, ArH), 4.73 (br q, J = 6.5 Hz, 2 H, CH_2), 3.52 (br q, J = 6.0 Hz, 2 H, CH_2), 2.54 (t, J = 7.3 Hz, 2 H, CH_2), 2.49 (s, 3 H, CH_3), 2.47 (t, J = 6.3 Hz, 2 H, CH_2), 2.24 (s, 3 H, CH_3), 2.01 (br quin, J = 7.1 Hz, 2 H, CH_2), 1.74 (br quin, J = 6.2 Hz, 2 H, CH_2); ^{13}C NMR δ 165.8, 154.4, 150.8 (2), 149.4, 146.2, 145.4, 138.9, 137.7, 137.6, 136.8, 134.3, 131.2, 130.0, 129.9, 127.9, 127.2, 121.7 (2), 120.1, 118.6, 117.0, 56.6, 55.7, 41.9, 41.3, 38.2, 27.7,

25.6, 21.4; HRMS (FAB^+) calcd for $C_{30}H_{33}N_8O_3$ (MH^+) *m/z* 553.2676, found 553.2669. Anal. calcd for $C_{30}H_{32}N_8O_3 \cdot \frac{1}{2}H_2O$: C, 64.2; H, 5.9; N, 20.0; found:C, 64.0; H, 5.7; N, 20.0 %.

Example Y

***N*-[3-(Methyl{3-[(7-methyl-1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]-1-phenazinecarboxamide (76).** Aqueous NH_3 (6 mL) was added to a solution of acetamide **73** (141 mg, 0.34 mmol) in MeOH (10 mL) and the mixture stirred at 20 °C for 18 h. The solvent was evaporated, the residue was dissolved in DMF (5 mL) and 1-(1*H*-imidazol-1-ylcarbonyl)phenazine (183 mg, 0.68 mmol) was added and mixture stirred at 20 °C for 48 h. The solvent was evaporated and the residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(0–4%) MeOH/DCM, to give compound **76** (178 mg, 100%) as a red solid, mp (DCM/hexane) 118–122 °C; ^{1}H NMR δ 10.86 (br s, 1 H, NH), 8.93 (dd, *J* = 7.0, 1.5, 1 H, ArH), 8.45 (br s, 1 H, NH), 8.34 (dd, *J* = 8.7, 1.5 Hz, 1 H, ArH), 8.21–8.27 (m, 2 H, ArH), 8.30 (s, 1 H, ArH), 7.99 (d, *J* = 8.8 Hz, 1 H, ArH), 7.93 (dd, *J* = 8.7, 7.2 Hz, 1 H, ArH), 7.79–7.83 (m, 2 H, ArH), 7.53 (dd, *J* = 8.9, 1.8 Hz, 1 H, ArH), 3.77 (br q, *J* = 6.4 Hz, 2 H, CH_2), 3.65 (br q, *J* = 5.9 Hz, 2 H, CH_2), 2.67 (t, *J* = 7.4 Hz, 2 H, CH_2), 2.62 (t, *J* = 6.1 Hz, 2 H, CH_2), 2.49 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 2.09 (br quin, *J* = 7.1 Hz, 2 H, CH_2), 1.88 (br quin, *J* = 6.2 Hz, 2 H, CH_2); ^{13}C NMR δ 165.1, 149.4, 143.4, 142.9, 141.3, 140.8, 137.8, 137.7, 136.7, 135.1, 135.0, 133.4, 131.6, 131.0, 130.0, 129.8, 129.7, 129.0, 120.1, 116.8, 56.8, 55.8, 42.0, 41.5, 38.2, 27.5, 25.6, 21.4; HRMS (FAB^+) calcd for $C_{28}H_{31}N_8O_3$ (MH^+) *m/z* 527.2519, found 527.2512. Anal. calcd for $C_{28}H_{30}N_8O_3 \cdot \frac{1}{4}H_2O$: C, 63.3; H, 5.8; N, 21.1; found:C, 63.2, H, 5.9, N, 21.4%.

Example Z

9-Methyl-*N*-[3-({3-[(7-methyl-1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]-1-phenazinecarboxamide (77). Aqueous NH_3 (5 mL) was added to a solution of acetamide **73** (135 mg, 0.32 mmol) in MeOH (5 mL) and the solution stirred at 20 °C for 18 h. The solvent was evaporated, the residue dissolved in DMF (5 mL) and 1-(1*H*-imidazol-1-ylcarbonyl)-9-methylphenazine (172 mg, 0.6 mmol) was added and stirred at 20 °C for 48 h. The solvent was evaporated

and the residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(0–4%) MeOH/DCM, to give compound **77** (147 mg, 91%) as a red solid, mp (DCM/hexane) 119–122 °C; ^{1}H NMR δ 11.02 (br s, 1 H, NH), 8.97 (dd, J = 7.2, 1.5 Hz, 1 H, ArH), 8.37 (dd, J = 8.5, 1.4 Hz, 1 H, ArH), 8.22 (br s, 1 H, NH), 8.10 (d, J = 8.7 Hz, 1 H, ArH), 8.05 (s, 1 H, ArH), 8.02 (d, J = 8.9 Hz, 1 H, ArH), 7.96 (dd, J = 8.7, 7.2 Hz, 1 H, ArH), 7.78 (dd, J = 8.6, 6.9 Hz, 1 H, ArH), 7.69–7.73 (m, 1 H, ArH) 7.55 (dd, J = 8.9, 1.6 Hz, 1 H, ArH), 3.77 (br q, J = 6.6 Hz, 2 H, CH_2), 3.65 (br q, J = 6.0 Hz, 2 H, CH_2), 2.93 (s, 3 H, CH_3), 2.61 (t, J = 7.3 Hz, 2 H, CH_2), 2.58 (t, J = 6.1 Hz, 2 H, CH_2), 2.49 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3), 2.07 (br quin, J = 7.2 Hz, 2 H, CH_2), 1.86 (br quin, J = 6.2 Hz, 2 H, CH_2); ^{13}C NMR δ 165.1, 149.4, 143.2, 143.1, 141.0, 139.7, 137.8, 137.7, 136.8, 136.6, 135.1, 133.3, 131.0, 130.9, 130.0, 129.9, 129.4, 127.7, 120.1, 116. 9, 56.4, 55.8, 42.0, 41.2, 38.3, 27.9, 25.7, 21.4, 18.1; HRMS (FAB$^+$) calcd for $C_{29}H_{33}N_8O_3$ (MH$^+$) m/z 541.2676, found 541.2669. Anal. calcd for $C_{29}H_{32}N_8O_3 \cdot \frac{1}{4}H_2O$: C, 63.9; H, 6.0; N, 20.6; found:C, 63.8; H, 5.9; N, 20.8%.

Example AA

***N*-[3-(Methyl{3-[(6-methyl-1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]-4-acridinecarboxamide (85).**

6-Methyl-1,2,4-benzotriazin-3-ol 1-Oxide (79). $NaNO_2$ (2.5 g, 36.3 mmol) was added in small portions to a stirred solution of 6-methyl-1,2,4-benzotriazin-3-amine 1-oxide (**78**) [Hay et. al., *J. Med Chem*. **2003**, 46, 169-182] (3.2 g, 18.2 mmol) in TFA (15 mL) at –5 to 0 °C. After the addition was completed the reaction mixture was stirred for further 1 h and poured into ice (150 g). The resulting pale yellow precipitate was filtered, washed with water and dried to give compound **79** (3.2 g, 97%), which was used without further purification.

3-Chloro-6-methyl-1,2,4-benzotriazine 1-Oxide (80). Compound **79** (3.2 g, 17.8 mmol) was heated at reflux in $POCl_3$ (25 mL) for 3 h. Excess reagent was evaporated and the residue was stirred in ice/water (150 mL) for 20 min. The resulting precipitate was filtered, air dried and purified by chromatography, eluting with a gradient (50–100%) of DCM/pet. ether, to give chloride **80** (2.5 g, 79%) as a white crystalline solid, mp (DCM/hexane) 156–158 °C; ^{1}H NMR δ 8.30 (d, J = 8.8 Hz, 1 H, H-8), 7.75

(br s, 1 H, H-5), 7.64 (dd, J = 9.4, 1.6 Hz, 1 H, H-7), 2.62 (s, 3 H, CH_3). Anal. calcd for $C_8H_6ClN_3O$: C, 49.1; H, 3.1; N, 21.5; found:C, 49.2; H, 3.1; N, 21.5%.

***tert*-Butyl 3-(Methyl{3-[(6-methyl-1-oxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propylcarbamate (81).** A mixture of chloride **80** (2.23 g, 11.4 mmol), *tert*-butyl-3[(aminopropyl)(methyl)amino]propylcarbamate **69** (Huang et al., *J. Med. Chem.* **1992**, 35, 2414-18) (3.34 g, 14.4 mmol) and triethylamine (2.3 mL, 16.5 mmol) in DME (60 mL) was heated at 85 °C for 3 h. The solvent was evaporated, the residue was dissolved in DCM (100 mL) and washed with aqueous NH_3 (40 mL). The organic layer was separated, the aqueous layer further extracted with DCM (3 × 30 mL), the combined organic fraction dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(0–5%) MeOH/DCM to give carbamate **81** (3.7 g, 80%) as a yellow solid, mp (DCM/hexane) 117–120 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.01 (d, J = 8.7 Hz, 1 H, H-8), 7.84 (br s, 1 H, NH), 7.37 (br s, 1 H, H-5), 7.15 (dd, J = 8.8, 1.7 Hz, 1 H, H-7), 6.75 (t, J = 5.2 Hz, 1 H, NH), 3.33–3.37 (m, 2 H, CH_2), 2.94 (br q, J = 6.5 Hz, 2 H, CH_2), 2.42 (s, 3 H, CH_3), 2.35 (t, J = 6.9 Hz, 2 H, CH_2), 2.28 (t, J = 7.0 Hz, 2 H, CH_2), 2.08 (s, 3 H, CH_3), 1.70 (br quin, J = 6.9 Hz, 2 H, CH_2), 1.51 (br quin, J = 6.9 Hz, 2 H, CH_2), 1.35 (s, 9 H, 3 × CH_3); ^{13}C NMR [$(CD_3)_2SO$] 159.0, 155.5, 148.5, 146.6, 128.2, 126.4, 124.8, 119.5, 77.2, 54.8, 54.7, 41.6, 39.0, 38.2, 28.1 (3), 27.1, 26.1, 21.3; HRMS (FAB$^+$) calcd for $C_{20}H_{33}N_6O_3$ (MH$^+$) m/z 405.2614, found 405.2616.

N^1-(3-Aminopropyl)-N^1-methyl-N^3-(6-methyl-1-oxido-1,2,4-benzotriazin-3-yl)-1,3-propanediamine (82). Carbamate **81** (2.1 g, 5.19 mmol) was dissolved in methanolic HCl (50 mL) and stirred 48 h at 20 °C. Excess reagent and solvent were evaporated and the residue partitioned between DCM and aqueous NH_3. The organic layer was separated and the aqueous layer was further extracted with DCM (4 × 30 mL). The combined organic fraction was dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(3–7%) MeOH/DCM, to give amine **82** (1.57 g, 99%) as a yellow solid, mp 118–122 °C (DCM/MeOH); ^{1}H NMR [$(CD_3)_2SO$] δ 8.01 (d, J = 8.8 Hz, 1 H, H-8), 7.87 (br s, 1 H, NH), 7.37 (br s, 1 H, H-5), 7.16 (dd, J = 8.8, 1.7 Hz, 1 H, H-7),

3.14–3.34 (m, 4 H, CH_2, NH_2), 2.54 (t, J = 6.5 Hz, 2 H, CH_2), 2.42 (s, 3 H, CH_3), 2.35 (t, J = 6.9 Hz, 2 H, CH_2), 2.31 (t, J = 7.2 Hz, 2 H, CH_2), 2.13 (s, 3 H, CH_3), 1.71 (br quin, J = 7.0 Hz, 2 H, CH_2), 1.47 (br quin, J = 7.0 Hz, 2 H, CH_2); HRMS (FAB^+) calcd for $C_{15}H_{25}N_6O$ (MH^+) m/z 305.2090, found 305.2088.

2,2,2-Trifluoro-*N*-[3-(methyl{3-[(6-methyl-1-oxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]acetamide (83). CF_3CO_2Et (0.88 mL, 7.4 mmol) and H_2O (0.13 ml, 7.4 mmol) were added to a stirred solution of amine **82** (1.5 g, 4.9 mmol) in CH_3CN (50 mL) and the reaction mixture heated at reflux for 20 h. The solvent was evaporated and the residue partitioned between DCM and aqueous $NaHCO_3$. The organic layer was separated, the aqueous layer further extracted with DCM (3 × 30 mL), the combined organic fraction dried, and the solvent evaporated to give acetamide **83** (1.9 g, 100%) as a yellow solid, mp (DCM/hexane) 127–130 °C; ^1H NMR [$(CD_3)_2SO$] δ 9.43 (br s, 1 H, NH), 8.01 (d, J = 8.8 Hz, 1 H, H-8), 7.85 (br s, 1 H, NH), 7.36 (br s, 1 H, H-5), 7.15 (dd, J = 8.8, 1.5 Hz, 1 H, H-7), 3.23 (br q, J = 6.5 Hz, 2 H, CH_2), 2.43 (s, 3 H, CH_3), 2.38 (t, J = 6.9 Hz, 2 H, CH_2), 2.32, (t, J = 6.9 Hz, 2 H, CH_2), 2.15 (s, 3 H, CH_3), 1.72 (br quin, J = 7.0 Hz, 2 H, CH_2), 1.64 (br quin, J = 7.0 Hz, 2 H, CH_2), CH_2 not observed; ^{13}C NMR [$(CD_3)_2SO$] δ 159.0, 156.0 (q, J = 36 Hz), 148.5, 146.6, 128.2, 126.4, 124.8, 119.5, 115.9 (q, J = 288 Hz), 54.7, 54.5, 41.5, 38.9, 37.7, 26.1, 25.8, 21.3; HRMS (FAB^+) calcd for $C_{17}H_{24}F_3N_6O_2$ (MH^+) 401.1913, found 401.1896. Anal. calcd for $C_{17}H_{23}F_3N_6O_2$: C, 51.0; H, 5.8; F, 14.2; N, 21.0; found:C, 51.1; 6.0; F, 14.2; N, 21.0%.

2,2,2-Trifluoro-*N*-[3-(methyl{3-[(6-methyl-1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]acetamide (84). A solution of trifluoroperacetic acid [prepared from trifluoroacetic anhydride (5.7 mL, 6.3 mmol) and 70% H_2O_2 (2.0 mL, 6.3 mmol) in DCM (10 mL)] was added to a suspension of acetamide **83** (1.63 g, 4.1 mmol) and trifluoroacetic acid (0.63 mL, 8.1 mol) in DCM (20 mL) and the mixture stirred at 20 °C for 18 h. The mixture was slowly added to a cooled solution of aqueous $NaHCO_3$ (100 mL). The organic layer was separated and the aqueous layer extracted further with DCM (4 × 30mL). The combined organic fraction was dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give (i) starting material **83** (807 mg, 49%) and

(ii) dioxide **84** (509 mg, 30%) as a red solid, mp (DCM/hexane) 128–131 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.43 (br s, 1 H, NH), 8.42 (t, J = 6.0 Hz, 1 H, NH), 8.32 (d, J = 8.9 Hz, 1 H, H-8), 7.93 (s, 1 H, H-5), 7.38 (dd, J = 9.0, 1.7 Hz, 1 H, H-7), 3.43 (br q, J = 6.6 Hz, 2 H, CH_2), 3.22 (br q, J = 6.6 Hz, 2 H, CH_2), 2.53 (s, 3 H, CH_3), 2.38 (t, J = 6.7 Hz, 2 H, CH_2), 2.31 (t, J = 6.9 Hz, 2 H, CH_2), 2.15 (s, 3 H, CH_3), 1.75 (br quin, J = 6.9 Hz, 2 H, CH_2), 1.65 (br quin, J = 7.0 Hz, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 155.9 (q, J = 36 Hz), 149.8, 146.9, 138 0, 128.8, 128.2, 120.8, 116.1 (q, J = 288 Hz), 115.5, 54.9, 54.6, 41.5, 39.5, 37.7, 26.0, 25.8, 21.6; HRMS (FAB$^+$) calcd for $C_{17}H_{24}F_3N_6O_3$ (MH$^+$) m/z 417.1862, found 417.1868. Anal. calcd for $C_{17}H_{23}F_3N_6O_3$: C, 49.0; H, 5.6; F, 13.7; N, 20.2; found:C, 49.3; H, 5.9; F, 14.0; N, 20.4%.

***N*-[3-(Methyl{3-[(6-methyl-1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]-4-acridinecarboxamide (85).** Aqueous NH_3 (5 mL) was added to a solution of dioxide **84** (125 mg, 0.3 mmol) in MeOH (5 mL) and the reaction mixture was stirred at 20 °C for 18 h. The solvent was evaporated, the residue was dissolved in DMF (5 mL), 4-(1*H*-imidazol-1-ylcarbonyl)acridine (164 mg, 0.6 mmol) was added and the mixture stirred at 20 °C for 48 h. The solvent was evaporated and the residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(0–5%) MeOH/DCM, to give compound **85** (148 mg, 94%) as a red solid, mp (DCM/hexane) 158–160 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.30 (t, J = 5.4 Hz, 1 H, NH), 9.23 (s, 1 H, ArH), 8.67 (dd, J = 7.1, 1.4 Hz, 1 H, ArH), 8.48 (t, J = 5.7 Hz, 1 H, NH), 8.32 (dd, J = 8.4, 1.2 Hz, 1 H, ArH), 8.23 (d, J = 8.7 Hz, 1 H, ArH), 8.17 (d, J = 8.4 Hz, 1 H, ArH), 8.00 (d, J = 8.9 Hz, 1 H, ArH), 7.92 (ddd, J = 7.7, 7.3, 1.4 Hz, 1 H, ArH), 7.76 (s, 1 H, ArH), 7.71 (t, J = 7.7 Hz, 1 H, ArH), 7.65 (t, J =7.4 Hz, 1 H, ArH), 7.31 (dd, J = 9.0, 1.5 Hz, 1 H, ArH), 3.59 (br q, J = 6.3 Hz, 2 H, CH_2), 3.42 (br q, J = 6.4 Hz, 2 H, CH_2), 2.57 (t, J = 7.0 Hz, 2 H, CH_2), 2.47 (t, J = 6.6 Hz, 2 H, CH_2), 2.44 (s, 3 H, CH_3), 2.23 (s, 3 H, CH_3), 1.92 (br quin, J = 6.9 Hz, 2 H, CH_2), 1.79 (br quin, J = 6.6 Hz, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 164.7, 149.6, 146.9, 146.8, 145.4, 138.4, 137.7, 134.3, 132.6, 131.8, 128.7, 128.6, 128.4, 128.3, 128.0, 126.4, 126.3, 125.5, 125.1, 120.7, 115.2, 55.4, 55.1, 41.7, 39.8, 37.4, 27.0, 25.8, 21.5; HRMS (FAB$^+$) calcd for $C_{29}H_{32}N_7O_3$ (MH$^+$) m/z 526.2567, found 526.2535. Anal. calcd for $C_{29}H_{31}N_7O_3$: C, 66.3; H, 5.9; N, 18.7; found:C, 66.0; H, 6.0; N, 18.8%.

Example AB

***N*-[3-(Methyl{3-[(6-methyl-1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]-2-(4-pyridinyl)-8-quinolinecarboxamide (86).** Aqueous NH_3 (5 mL) was added to a solution of dioxide **84** (126 mg, 0.3 mmol) in MeOH (5 mL) and the mixture stirred at 20 °C for 18 h. The solvent was evaporated, the residue dissolved in DMF (5 mL), 8-(1*H*-imidazol-1-ylcarbonyl)-2-(4-pyridinyl)quinoline (150 mg, 0.6 mmol) was added and the mixture stirred at 20 °C for 48 h. The solvent was evaporated, the residue dissolved in DCM (20 mL) and washed with water (3 × 15 mL). The organic layer was separated, dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(0–3%) MeOH/DCM, to give compound **86** (165 mg, 100%) as a red solid, mp (DCM/hexane) 178–180 °C; ^{1}H NMR δ 10.81 (br s, 1 H, NH), 8.77–8.83 (m, 3 H, ArH), 8.40 (br s, 1 H, NH), 8.32 (d, J = 8.6 Hz, 1 H, ArH), 8.13 (d, J = 8.9 Hz, 1 H, ArH), 7.87–7.93 (m, 5 H, ArH), 7.65 (t, J = 7.7 Hz, 1 H, ArH), 7.21 (d, J = 8.8 Hz, 1 H, ArH), 3.72 (br q, J = 6.3 Hz, 2 H, CH_2), 3.49 (br q, J = 5.3 Hz, 2 H, CH_2), 2.54 (t, J = 7.2 Hz, 2 H, CH_2), 2.47 (s, 3 H, CH_3), 2.46 (t, J = 6.2 Hz, 2 H, CH_2), 2.24 (s, 3 H, CH_3), 2.01 (br quin, J = 5.5 Hz, 2 H, CH_2), 1.72 (br quin J = 6.1 Hz, 2 H, CH_2); ^{13}C NMR δ 165.9, 154.4 (2), 150.8, 149.8, 147.6, 146.2, 145.3, 138.8, 138.1, 134.1, 131.1, 130.3, 128.8, 128.5, 127.8, 127.2, 121.7 (2), 121.3, 118.5, 116.0, 56.7, 55.7, 41.9, 41.3, 38.2, 27.7, 25.5, 22.2; HRMS (FAB^+) calcd for $C_{30}H_{33}N_8O_3$ (MH^+) m/z 553.2676, found 553.2673. Anal. calcd for $C_{30}H_{32}N_8O_3\cdot\frac{1}{2}H_2O$: C, 64.2; H, 5.9; N, 20.0; found:C, 64.4; H, 6.1; N, 19.5%.

Example AC

***N*-[3-(Methyl{3-[(6-methyl-1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]-1-phenazinecarboxamide (87).** Aqueous NH_3 (6 mL) was added to a solution of dioxide **84** (145 mg, 0.35 mmol) in MeOH (10 mL) and stirred at 20 °C for 18 h. The solvent was evaporated, the residue dissolved in DMF (5 mL), 1-(1*H*-imidazol-1-ylcarbonyl)phenazine (183 mg, 0.68 mmol) was added and the mixture stirred at 20 °C for 48 h. The solvent was evaporated and the residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(0–4%) MeOH/DCM, to give compound **87** (181 mg, 98%) as a red solid, mp (DCM/hexane) 111–114 °C; ^{1}H NMR δ 10.82 (br s, 1 H, NH), 8.91 (dd, J = 7.2, 1.5

Hz, 1 H, ArH), 8.59 (br s, 1 H, NH), 8.33 (dd, J = 8.6, 1.5 Hz, 1 H, ArH), 8.21–8.25 (m, 2 H, ArH), 8.13 (d, J = 8.9 Hz, 1 H, ArH), 7.93 (dd, J = 8.7, 7.1 Hz, 1 H, ArH), 7.85–7.90 (m, 2 H, ArH), 7.83 (s, 1 H, ArH), 7.22 (dd, J = 9.0, 1.7 Hz, 1 H, ArH), 3.78 (br q, J = 6.4 Hz, 2 H, CH_2), 3.65 (br q, J = 5.9 Hz, 2 H, CH_2), 2.69 (t, J = 7.3 Hz, 2 H, CH_2), 2.63 (t, J = 6.1 Hz, 2 H, CH_2), 2.45 (s, 3 H, CH_3), 2.36 (s, 3 H, CH_3), 2.10 (br quin, J = 7.1 Hz, 2 H, CH_2), 1.89 (br quin, J = 6.2 Hz, 2 H, CH_2); ^{13}C NMR δ 165.1, 149.8, 147.8, 143.3, 142.9, 141.4, 140.8, 138.0, 135.0, 134.9, 133.3, 131.6, 131.0, 130.0 (2), 129.0, 129.7, 129.0, 121.3, 115.7, 56.9, 55.8, 42.0, 41.6, 38.2, 27.5, 25.5, 22.2; HRMS (FAB$^+$) calcd for $C_{28}H_{31}N_8O_3$ (MH$^+$) m/z 527.2519, found 527.2506. Anal. calcd for $C_{28}H_{30}N_8O_3 \cdot \frac{1}{4}H_2O$: C, 63.3; H, 5.8; N, 21.1; found:C, 63.3; H, 5.8; N, 21.5%.

Example AD

9-Methyl-*N*-[3-({3-[(6-methyl-1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]-1-phenazinecarboxamide (88). Aqueous NH_3 (5 mL) was added to a solution of dioxide **84** (126 mg, 0.3 mmol) in MeOH (5 mL) and the reaction mixture was stirred at 20 °C for 18 h. The solvent was evaporated, the residue dissolved in DMF (5 mL), 1-(1*H*-imidazol-1-ylcarbonyl)-9-methylphenazine (172 mg, 0.6 mmol) was added and the mixture stirred at 20 °C for 48 h. The solvent was evaporated and the residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(0–4%) MeOH/DCM, to give compound **88** (147 mg, 91%) as a red solid, mp (DCM/hexane) 80–83 °C; ^{1}H NMR δ 10.99 (t, J = 5.2 Hz, 1 H, NH), 8.96 (dd, J = 7.1, 1.5 Hz, 1 H, ArH), 8.43 (br s, 1 H, NH), 8.36 (dd, J = 8.5, 1.0 Hz, 1 H, ArH), 8.14 (d, J = 8.9 Hz, 1 H, ArH), 8.10 (dd, J = 8.8, 1.2 Hz, 1 H, ArH), 7.96 (dd, J = 8.8, 7.1 Hz, 1 H, ArH), 7.96 (dd, J = 8.7, 6.8 Hz, 1 H, ArH), 7.77 (dd, J = 8.7, 6.8 Hz, 1 H, ArH), 7.69–7.73 (m, 1 H, ArH), 7.22 (dd, J = 8.9, 1.8 Hz, 1 H, ArH), 3.77 (br q, J = 6.6 Hz, 2 H, CH_2), 3.66 (br q, J = 6.1 Hz, 2 H, CH_2), 2.93 (s, 3 H, CH_3), 2.62 (t, J = 7.2 Hz, 2 H, CH_2), 2.58 (t, J = 6.0 Hz, 2 H, CH_2), 2.48 (s, 3 H, CH_3), 2.32 (s, 3 H, CH_3), 2.08 (br quin, J = 7.2 Hz, 2 H, CH_2), 1.86 (br quin, J = 6.2 Hz, 2 H, CH_2); ^{13}C NMR δ 165.2, 149.8, 147.8, 143.1 (2), 141.0, 139.7,138.1, 136.6, 135.0, 133.3, 131.0, 130.9, 130.0, 129.5, 129.0, 128.5, 127.7, 121.3, 115.8, 56.4, 55.8, 42.0, 41.3, 38.3, 27.9, 25.7, 22.3, 18.1; HRMS (FAB$^+$) calcd for $C_{29}H_{33}N_8O_3$ (MH$^+$) m/z 541.2676, found 541.2668.

Example AE

***N*-{2-[{2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethyl}(methyl)amino]ethyl}-4-acridinecarboxamide (95).**

***tert*-Butyl 2-[(2-Aminoethyl)(methyl)amino]ethylcarbamate (90).** A solution of $(BOC)_2O$ (9.60 g, 44 mmol) in THF (50 mL) was added over a period of 2 h to a solution of bis(diethylamino)methylamine (**89**) (10.32 g, 88 mmol) in THF (50 mL) at 0 °C. The reaction mixture stirred for 30 min then allowed to warm to 20 °C and stirred for 20 h. The reaction mixture was partitioned between DCM and saturated aqueous NaCl, the organic layer separated and the aqueous layer further extracted with DCM (3 × 25 mL). The combined organic extract was dried and the solvent evaporated at 30 °C to give carbamate **90** (8.79 g, 46%) as a colourless oil, which was used without further purification.

***tert*-Butyl 2-(Methyl{2-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]ethyl}amino)ethylcarbamate (91).** A solution of chloride **3** (2.0 g, 11.0 mmol), carbamate **90** (2.9 g, 13.3 mmol) and triethylamine (3.0 mL, 22.1 mmol) in DME (50 mL) was heated at 85 °C for 3 h. The solvent was evaporated and the residue was partitioned between DCM (100 mL) and aqueous NH_3 (50 mL). The DCM layer was separated, the aqueous layer further extracted with DCM (3 × 30 mL), the combined organic fraction dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(0–5%) MeOH/DCM, to give (i) starting material **3** (500 mg, 25%) and (ii) carbamate **91** (2.1 g, 52%) as a yellow solid, mp (DCM/hexane) 122–124 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.13 (dd, J = 8.6, 1.0 Hz, 1 H, H-8), 7.78 (ddd, J = 8.4, 7.0, 1.6 Hz, 1 H, H-6), 7.71 (br s, 1 H, NH), 7.52 (d, J = 8.2 Hz, 1 H, H-5), 7.33 (ddd, J = 7.8, 7.1, 1.2 Hz, 1 H, H-7), 6.61 (br s, 1 H, NH), 3.43 (br q, J = 6.0 Hz, 2 H, CH_2), 3.01 (br q, J = 6.2 Hz, 2 H, CH_2), 2.57 (t, J = 6.6 Hz, 2 H, CH_2), 2.42 (t, J = 6.7 Hz, 2 H, CH_2), 2.23 (s, 3 H, CH_3), 1.35 (s, 9 H, 3 × CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 158.8, 155.4, 148.2, 135.6, 129.9, 126.0, 124.4, 119.8, 77.4, 56.4, 55. 5, 41.8, 38.5, 37.8, 28.1 (3); HRMS (FAB^+) calcd for $C_{17}H_{27}N_6O_3$ (MH^+) m/z 363.2145, found 363.2144. Anal. calcd for $C_{17}H_{26}N_6O_3$: C, 56.3; H, 7.2; N, 23.2; found:C, 56.5; H, 7.3; N, 23.3%.

***N*¹-(2-Aminoethyl)-*N*¹-methyl-*N*²-(1-oxido-1,2,4-benzotriazin-3-yl)-1,2-ethanediamine (92).** Carbamate **91** (2.14 g, 5.9 mmol) was dissolved in methanolic HCl (30 mL) and stirred 20 h at 20 °C. Excess reagent and solvent were evaporated and the residue was partitioned between DCM and aqueous NH_3. The organic fraction was separated and the aqueous faction was further extracted with DCM (4 × 30 mL). The combined organic fraction was dried and the solvent evaporated to give amine **92** (1.55 g, 100%) as yellow solid which was used without further purification, ^{1}H NMR [$(CD_3)_2SO$] δ 8.13 (dd, J = 8.6, 1.3 Hz, 1 H, H-8), 7.78 (ddd, J = 7.7, 7.0, 1.4 Hz, 2 H, H-6, NH), 7.57 (d, J = 8.4 Hz, 1 H, H-5), 7.33 (ddd, J = 7.8, 7.1, 1.3 Hz, 1 H, H-7), 3.42–3.68 (m, 2 H, CH_2), 3.20–3.40 (m, 2 H, CH_2), 2.58 (q, J = 6.9 Hz, 2 H, CH_2), 2.37 (t, J = 6.5 Hz, 2 H, CH_2), 2.22 (s, 3 H, CH_3), 1.42 (br s, 2 H, NH_2).

2,2,2-Trifluoro-*N*-[2-(methyl{2-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]ethyl}amino)ethyl]acetamide (93). CF_3CO_2Et (2.05 mL, 17.2 mmol) and H_2O (0.31 ml, 17.2 mmol) was added to a solution of amine **92** (1.5 g, 5.7 mmol) in CH_3CN (50 mL) and the reaction mixture was heated at reflux for 48 h. The reaction mixture was evaporated and residue partitioned between DCM and aqueous $NaHCO_3$. The DCM layer was separated and the aqueous layer was further extracted with DCM (5 × 30 mL). The combined organic fraction was dried and the solvent evaporated to give trifluoroacetamide **93** (1.80 g, 88%) as a yellow solid, mp (DCM/hexane) 141–143 °C; ^{1}H NMR [$(CD_3)SO$] δ 9.29 (br s, 1 H, NH), 8.13 (dd, J = 8.6, 1.3 Hz, 1 H, H-8), 7.78 (ddd, J = 8.4, 7.0, 1.5 Hz, 1 H, H-6), 7.68 (br s, 1 H, NH), 7.57 (d, J = 8.4 Hz, 1 H, H-5), 7.33 (ddd, J = 8.5, 7.1, 1.3 Hz, 1 H, H-7), 3.42 (br q, J = 6.3 Hz, 2 H, CH_2), 3.30 (br q, J = 6.8 Hz, 2 H, CH_2), 2.61 (t, J = 6.7 Hz, 2 H, CH_2), 2.56 (t, J = 6.7 Hz, 2 H, CH_2), 2.27 (s, 3 H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 158.8, 156.1 (q, J = 36 Hz) 148.3, 135.6, 130.0, 125.9, 124.4, 119.8, 115.8 (q, J = 288 Hz), 55.4, 55.1, 41.7, 38.4, 37.2; HRMS (FAB$^+$) calcd for $C_{14}H_{18}F_3N_6O_2$ (MH^+) m/z 359.1443, found 359.1451. Anal. calcd for $C_{14}H_{17}F_3N_6O_2$: C, 46.9; H, 4.8; N, 23.5; F, 15.9; found:C, 47.2; H, 4.9; N, 23.6; F, 15.8%.

***N*-{2-[{2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethyl}(methyl)amino]ethyl}-2,2,2-trifluoroacetamide (94).** A solution of trifluoroperacetic acid [prepared from trifluoroacetic anhydride (6.8 mL, 49 mmol)

and 70% H_2O_2 (2.0 mL, 49 mmol) in DCM (20 mL)] was added to a solution of trifluoroacetamide **93** (1.75 g, 4.9 mmol) and trifluoroacetic acid (0.8 mL, 9.8 mmol) in DCM (20 mL) and the reaction mixture was stirred at 20 °C for 5 h. The reaction mixture was slowly added to a cooled solution of aqueous $NaHCO_3$ (100 mL). The DCM layer was separated and the aqueous layer was further extracted with DCM (5 × 30 mL). The combined organic fraction was dried and the solvent was evaporated. The residue was purified by chromatography, eluting with a gradient (0–4%) of DCM/MeOH, to give (i) starting material **93** (100 mg, 6%); and (ii) dioxide **94** (859 mg, 47%) as a red solid, mp (DCM/hexane) 141–144 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.28 (br s, 1 H, NH), 8.20 (d, J = 9.1 Hz, 1 H, H-5), 8.12 (d, J = 8.6 Hz, 1 H, H-8), 8.03 (t, J = 5.8 Hz, 1 H, NH), 7.96 (ddd, J = 8.6, 7.2, 1.3 Hz, 1 H, H-6), 7.56 (ddd, J = 8.6, 7.1, 1.3 Hz, 1 H, H-7), 3.48 (br q, J = 6.3 Hz, 2 H, CH_2), 3.31 (br q, J = 6.3 Hz, 2 H, CH_2), 2.63, (t, J = 6.6 Hz, 2 H, CH_2), 2.54 (t, J = 6.8 Hz, 2 H, CH_2), 2.27 (s, 3 H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 156.1 (q, J = 36 Hz), 149.7, 138.0, 135.4, 129.9, 126.9, 121.0, 115.8 (q, J = 288 Hz), 116.7, 55.4, 55.0, 41.6, 38.3, 37.1; HRMS (FAB^+) calcd for $C_{14}H_{18}F_3N_6O_3$ (MH^+) m/z 375.1393, found 375.1392. Anal. calcd for $C_{14}H_{17}F_3N_6O_3$: C, 44.9; H, 4.6; N, 22.5; found:C, 44.8; H, 4.6; N, 22.5%.

***N*-{2-[{2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethyl}(methyl)amino]ethyl}-4-acridinecarboxamide (95).** Aqueous NH_3 (6 mL) was added to a solution of dioxide **94** (125 mg, 0.33 mmol) in MeOH (6 mL) and the reaction mixture was stirred at 20 °C for 16 h. The solvent was evaporated, the residue dissolved in THF (5 mL), 4-(1*H*-imidazol-1-ylcarbonyl)acridine (180 mg, 0.66 mmol) was added and the mixture stirred at 20 °C for 48 h. The solvent was evaporated, the residue was dissolved in DCM (20 mL) and washed with water (3 × 15 mL). The organic fraction was dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(0–3%) MeOH/DCM, to give compound **95** (132 mg, 94%) as a red solid, mp (DCM/hexane) 160–162 °C; ^{1}H NMR δ 11.90 (br s, 1 H, NH), 8.95 (dd, J = 7.1, 1.5 Hz, 1 H, ArH), 8.72 (s, 1 H, ArH), 8.16 (d, J = 8.6 Hz, 1 H, ArH), 8.12 (d, J = 8.8 Hz, 1 H, ArH), 8.07 (dd, J = 8.4, 1.4 Hz, 1 H, ArH), 7.82–7.86 (m, 2 H, ArH), 7.78 (ddd, J = 7.7, 6.7, 1.5 Hz, 1 H, ArH), 7.70 (ddd, J = 7.8, 7.1, 1.3 Hz, 1 H, ArH), 7.64 (dd, J = 8.2, 7.1 Hz, 1 H, ArH), 7.46 (ddd, J = 7.5, 7.2, 0.7 Hz, 1 H, ArH), 7.40 (ddd, J =

7.9, 7.1, 1.3 Hz, 1 H, ArH), 7.29 (br s, 1 H, NH), 3.86 (br q, J = 6.0 Hz, 2 H, CH_2), 3.70 (br q, J = 5.6 Hz, 2 H, CH_2), 2.93 (t, J = 6.4 Hz, 2 H, CH_2), 2.89 (t, J = 6.1 Hz, 2 H, CH_2), 2.57 (s, 3 H, CH_3); ^{13}C NMR δ 166.0, 149.7, 147.4, 146.5, 137.8, 137.4, 135.3, 135.0, 132.1, 131.1, 130.1, 128.8, 128.6, 127.9, 126.8, 126.7, 126.1, 125.8, 125.5, 121.5, 117.2, 56.5, 55.9, 42.5, 39.1, 37.8; HRMS (FAB$^+$) calcd for $C_{26}H_{26}N_7O_3$ (MH$^+$) m/z 484.2097, found 484.2102.

Example AF

***N*-{2-[{2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethyl}(methyl)amino]ethyl}-2-(4-pyridinyl)-8-quinolinecarboxamide (96).** Aqueous NH_3 (6 mL) was added to a solution of dioxide **94** (132 mg, 0.35 mmol) in MeOH (10 mL) and the reaction mixture was stirred at 20 °C for 18 h. The solvent was evaporated, the residue dissolved in DMF (5 mL), 8-(1*H*-imidazol-1-ylcarbonyl)-2-(4-pyridinyl)quinoline (150 mg, 0.6 mmol) was added and the mixture stirred at 20 °C for 48 h. The solvent was evaporated, the residue was dissolved in DCM (20 mL) and washed with water (3 × 15 mL). The organic layer was separated, dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(0–3%) MeOH/DCM to give compound **96** (174 mg, 97%) as a red solid, mp (DCM/hexane) 130–135 °C; ^{1}H NMR δ 11.00 (t, J = 5.0 Hz, 1 H, NH), 8.83 (dd, J = 5.3, 2.2 Hz, 1 H, ArH), 8.81 (d, J = 7.7 Hz, 1 H, ArH), 8.81 (dd, J = 4.7, 3.0 Hz, 1 H, ArH), 8.29 (d, J = 8.6 Hz, 1 H, ArH), 8.23 (dd, J = 8.1 Hz, 1 H, ArH), 7.98 (d, J = 9.7 Hz, 1 H, ArH), 7.92–7.93 (m, 2 H, ArH), 7.87–7.90 (m, 2 H, ArH), 7.76 (ddd, J = 6.1, 5.4, 2.2 Hz, 1 H, ArH), 7.65 (dd, J = 7.4, 6.5 Hz, 1 H, ArH), 7.44 (ddd, J = 7.9, 7.0, 1.3 Hz, 1 H, ArH), 7.21 (br, 1 H, NH), 3.79 (br q, J = 6.1 Hz, 2 H, CH_2), 3.48 (br q, J = 5.8 Hz, 2 H, CH_2), 2.82 (t, J = 6.3 Hz, 2 H, CH_2), 2.73 (t, J = 6.1 Hz, 2 H, CH_2), 2.43 (s, 3 H, CH_3); ^{13}C NMR δ 165.8, 154.6 (2), 150.7, 149.6, 146.4, 145.4, 138.8, 138.0, 135.2, 134.5, 131.3, 130.2, 129.5, 127.9, 127.1, 126.9, 121.8 (2), 121.6, 118.7, 117.3, 56.8, 56.1, 42.3, 38.8, 37.9; HRMS (FAB$^+$) calcd for $C_{27}H_{27}N_8O_3$ (MH$^+$) m/z 511.2206, found 511.2208. Anal. calcd for $C_{27}H_{26}N_8O_3 \cdot \frac{1}{4}H_2O$: C, 63.0; H, 5.2; N, 21.8; found:C, 63.0; H, 5.2; N, 21.5%.

Example AG

N-{2-[{2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethyl}(methyl)amino]ethyl}-1-phenazinecarboxamide (97). Aqueous NH_3 (6 mL) was added to a solution of dioxide **94** (120 mg, 0.32 mmol) in MeOH (10 mL) and reaction mixture was stirred at 20 °C for 18 h. The solvent was evaporated, the residue dissolved in DMF (5 mL), and 1-(1H-imidazol-1-ylcarbonyl)phenazine (172 mg, 0.64 mmol) added and the mixture stirred at 20 °C for 48 h. The solvent was evaporated and the residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(0–3%) MeOH/DCM, to give compound **97** (137 mg, 88%) as a red solid, mp (DCM/hexane) 163–165 °C; ^{1}H NMR δ 11.07 (br s, 1 H, NH), 8.95 (dd, J = 7.1, 1.5 Hz, 1 H, ArH), 8.31 (dd, J = 8.7, 1,5 Hz, 1 H, ArH), 8.07–8.11 (m, 2 H, ArH), 8.03 (dd, J = 8.7, 0.7 Hz, 1 H, ArH), 7.93 (dd, J = 8.7, 7.1 Hz, 1 H, ArH), 7.78 (ddd, J = 7.7, 6.8, 1.6, 1 H, ArH), 7.65–7.72 (m, 2 H, ArH), 7.60 (dd, J = 8.6, 0.9 Hz, 1 H, ArH), 7.38 (ddd, J = 7.8, 7.0, 1.5 Hz, 1 H, ArH), 7.19 (br s, 1 H, NH), 3.85 (br q, J = 5.8 Hz, 2 H, CH_2), 3.68 (br q, J = 5.6 Hz, 2 H, CH_2), 2.85–2.91 (m, 4 H, 2 × CH_2), 2.57 (s, 3 H, CH_3); ^{13}C NMR δ 165.0, 149.6, 143.4, 142.7, 141.3, 141.0, 137.6, 135.2 (2), 133.4, 131.2, 130.5, 130.0, 129.9, 129.6, 129.5, 128.8, 126.9, 121.3, 117.0, 56.2, 55.8, 42.3, 38.9, 37.8; HRMS (FAB$^+$) calcd for $C_{25}H_{25}N_8O_3$ (MH$^+$) m/z 485.2050, found 485.2045. Anal calcd for $C_{25}H_{24}N_8O_3$: C, 62.0; H, 5.0; N, 23.1; found:C, 61.7; H, 4.7; N 23.1%.

Example AH

N-{2-[{2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethyl}(methyl)amino]ethyl}-9-methyl-1-phenazinecarboxamide (98). Aqueous NH_3 (6 mL) was added to a solution of dioxide **94** (120 mg, 0.32 mmol) in MeOH (10 mL) and the reaction mixture was stirred at 20 °C for 16 h. The solvent was evaporated, the residue dissolved in THF (5 mL), and 1-(1H-imidazol-1-ylcarbonyl)-9-methylphenazine (185 mg, 0.6 mmol) was added and the mixture stirred at 20 °C for 48 h. The solvent was evaporated and the residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(0–3%) MeOH/DCM, to give compound **98** (128 mg, 80%) as a red solid, mp (DCM/hexane) 161–163 °C; ^{1}H NMR δ 11.03 (br s, 1 H, NH), 8.94 (dd, J = 7.1, 1.5 Hz, 1 H, ArH), 8.29 (dd, J = 8.6, 1.5 Hz, 1 H, ArH), 8.12 (dt, J = 8.8, 0.7 Hz, 1 H, ArH), 7.94–7.98 (m, 1 H, ArH), 7.91 (dd, J = 8.6, 7.1 Hz, 1 H, ArH), 7.60–7.70 (m, 4 H, ArH), 7.78

(ddd, $J = 8.3$, 7.3, 1.1 Hz, 1 H, ArH), 7.26 (br s, 1 H, NH), 3.86 (br q, $J = 6.1$ Hz, 2 H, CH_2), 3.60 (br q, $J = 5.5$ Hz, 2 H, CH_2), 2.91 (s, 3 H, CH_3), 2.87 (t, $J = 6.2$ Hz, 2 H, CH_2), 2.80 (t, $J = 5.9$ Hz, 2 H, CH_2), 2.47 (s, 3 H, CH_3); ^{13}C NMR δ 165.2, 149.5, 143.1, 141.0, 140.0, 137.6, 136.7, 135.2, 135.1, 133.3, 130.7, 130.6, 129.9 (2), 129.4, 127.6, 126.8, 121.3, 117.0, 56.6, 55.8, 42.3, 38.8, 37.7, 17.9, one resonance not observed; HRMS (FAB$^+$) calcd for $C_{26}H_{27}N_8O_3$ (MH$^+$) m/z 499.2206, found 499.2200. Anal. calcd for $C_{26}H_{26}N_8O_3$: C, 62.6, H; 5.3; N, 22.5; found:C, 62.2; H, 5.3; N, 22.4%.

Example AI

***N*-{2-[{2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethyl}(methyl)amino]ethyl}-5-methyl-4-acridinecarboxamide (99).** Aqueous NH_3 (6 mL) was added to a solution of dioxide **94** (125 mg, 0.33 mmol) in MeOH (10 mL) and the reaction mixture was stirred at 20 °C for 24 h. The solvent was evaporated, the residue dissolved in THF (5 mL) and 4-(1*H*-imidazol-1-ylcarbonyl)-5-methylacridine (208 mg, 0.72 mmol) was added and the mixture stirred at 20 °C for 24 h. The solvent was evaporated, the residue dissolved in DCM (20 mL) and washed with water (3 × 15 mL). The organic layer was dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(0–4%) MeOH/DCM, to give compound **99** (180 mg, 100%) as a red solid, mp (DCM/hexane) 148–152 °C; ^{1}H NMR δ 11.90 (br s, 1 H, NH), 8.94 (dd, $J = 7.1$, 1.5 Hz, 1 H, ArH), 8.70 (s, 1 H, ArH), 8.17 (d, $J = 8.2$ Hz, 1 H, ArH), 8.05 (dd, $J = 8.3$, 1.4 Hz, 1 H, ArH), 7.88 (d, $J = 8.2$ Hz, 1 H, ArH), 7.96 (d, $J = 7.9$, Hz, 1 H, ArH), 7.69–7.73 (m, 1 H, ArH), 7.60–7.65 (m, 2 H, ArH), 7.38–7.43 (m, 2 H, ArH), 7.33 (br s, 1 H, NH), 3.85 (br q, $J = 6.3$ Hz, 2 H, CH_2), 3.61 (br q, $J = 4.2$ Hz, 2 H, CH_2), 2.90 (s, 3 H, CH_3), 2.89 (t, $J = 6.7$ Hz, 2 H, CH_2), 2.56 (t, $J = 6.0$ Hz, 2 H, CH_2), 2.47 (s, 3 H, CH_3); ^{13}C NMR δ 166.2, 149.7, 147.0, 145.4, 137.9, 137.8, 135.9, 135.2, 135.1, 132.1, 130.8, 130.1, 128.4, 126.7, 126.6, 126.2, 126.1, 125.8, 125.4, 121.5, 117.2, 56.9, 55.8, 42.3, 39.0, 37.9, 18.8; HRMS (FAB$^+$) calcd for $C_{27}H_{28}N_7O_3$ (MH$^+$) m/z 498.2254, found 498.2257. Anal. calcd for $C_{27}H_{27}N_7O_3 \cdot \frac{1}{4}H_2O$: C, 64.6; H, 5.5; N, 19.5; found:C, 64.5; H, 5.5; N, 19.7%.

Example AJ

N-{3-[{3-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}(methyl)amino]propyl}-1-phenazinecarboxamide (100). Aqueous NH_3 (6 mL) was added to a solution of trifluoroacetamide **39** (283 mg, 0.70 mmol) in MeOH (10 mL) and the reaction mixture was stirred at 20 °C for 18 h. The solvent was evaporated, the residue dissolved in DMF (5 mL), 1-(1*H*-imidazol-1-ylcarbonyl)phenazine (283 mg, 1.05 mmol) added and the mixture stirred at 20 °C for 48 h. The solvent was evaporated and the residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(0–3%) MeOH/DCM, to give compound **100** (293 mg, 82%) as a red solid, mp (DCM/hexane) 129–130 °C; ^{1}H NMR δ 10.85, (br s, 1 H, NH), 8.93 (dd, J = 7.1, 1.4 Hz, 1 H, ArH), 8.52 (br, 1 H, NH), 8.33 (dd, J = 8.7, 1.4 Hz, 1 H, ArH), 8.21–8.27 (m, 2 H, ArH), 8.11 (d, J = 8.7 Hz, 1 H, ArH), 7.93 (dd, J = 8.6, 6.5 Hz, 1 H, ArH), 7.86–7.90 (m, 3 H, ArH), 7.70 (t, J = 7.8 Hz, 1 H, ArH), 7.42 (t, J = 7.8 Hz, 1 H, ArH), 3.77 (br q, J = 6.4 Hz, 2 H, CH_2), 3.66 (br q, J = 5.7 Hz, 2 H, CH_2), 2.68 (t, J = 7.3 Hz, 2 H, CH_2), 2.62 (t, J = 6.1 Hz, 2 H, CH_2), 2.36 (s, 3 H, CH_3), 2.10 (br quin, J = 7.1 Hz, 2 H, CH_2), 1.89 (br quin, J = 6.2 Hz, 2 H, CH_2); ^{13}C NMR δ 165.0, 149.8, 143.4, 142.9, 141.4, 140.8, 138.2, 135.4, 135.1, 135.0, 133.4, 131.5, 130.9, 130.1 (2), 129.8, 129.0, 126.7, 121.6, 117.1, 56.7, 55.9, 42.1, 41.5, 38.2, 27.5, 25.6; HRMS (FAB$^+$) calcd for $C_{27}H_{29}N_8O_3$ (M^+) m/z 513. 2363, found 513.2365. Anal. calcd for $C_{27}H_{28}N_8O_3$: C, 54.8; H, 6.0; N, 31.9; found:C, 55.1; H, 5.8; N, 32.3%.

Example AK

N^1-(2-aminoethyl)-N^2-(1,4-dioxido-1,2,4-benzotriazin-3-yl)-1,2-ethanediamine (101). A solution of carbamate (**36**) (252 mg, 0.54 mmol) in methanolic HCl was stirred at 20 °C for 24 h. Excess reagent and solvent were evaporated and the residue partitioned between aqueous NH_3 and DCM. The organic layer was separated and the aqueous layer was extracted with DCM (15 × 20 mL). The combined organic extract was dried, and the solvent evaporated to give amine **101** (109 mg, 76%) as a gum which was used without further purification, ^{1}H NMR δ 8.33 (d, J = 8.7 Hz, 1 H, ArH), 8.30 (d, J = 8.8 Hz, 1 H, ArH), 7.87 (ddd, J = 8.5, 7.1, 1.0 Hz, 1 H, ArH), 7.50 (ddd, J = 8.4, 7.1, 1.2 Hz, 1 H, ArH), 3.70 (br t, J = 5.9 Hz, 2 H, CH_2), 2.98 (br t, J = 5.9 H, 2 H, CH_2), 2.84 (br t, J = 5.6 Hz, 2 H, CH_2), 2.74 (br t, J = 5.6 Hz, 2 H, CH_2), 2 × NH, NH_2 not observed.

***N*-[2-({2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethyl}amino)ethyl]-2-(4-pyridinyl)-8-quinolinecarboxamide (102).** 8-(1*H*-Imidazol-1-ylcarbonyl)-2-(4-pyridinyl)quinoline (198 mg, 0.78 mmol) was added to a solution of amine (**101**) (105 mg, 0.39 mmol) in DMF (10 mL) and the reaction mixture was stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–2%) of aqueous NH_3/(0–4%) MeOH/DCM to give compound **102** (148 mg, 75%) as a red solid, mp (DCM/hexane) 160–165 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.62 (t, J = 5.4 Hz, 1 H, NH), 8.75 (d, J = 6.1 Hz, 1 H, ArH), 8.75 (dd, J = 4.5, 1.8 Hz, 1 H, ArH), 8.68 (d, J = 8.7 Hz, 1 H, ArH), 8.57 (dd, J = 7.3, 1.6 Hz, 1 H, ArH), 8.28 (d, J = 8.7 Hz, 1 H, ArH), 8.21 (dd, J = 8.2, 1.6 Hz, 1 H, ArH), 8.18 (d, J = 6.2 Hz, 1 H, ArH), 8.15 (dd, J = 3.5, 1.7 Hz, 1 H, ArH), 8.11 (br s, 1 H, NH), 8.07 (dd, J = 8.6, 0.9 Hz, 1 H, ArH), 7.98 (dd, J = 8.8, 0.7 Hz, 1 H, ArH), 7.88 (ddd, J = 7.8, 7.0, 1.4 Hz, 1 H, ArH), 7.77 (dd, J = 8.0, 7.4 Hz, 1 H, ArH), 7.51 (ddd, J = 7.8, 7.0, 1.5 Hz, 1 H, ArH), 3.61 (br q, J = 5.8 Hz, 2 H, CH_2), 3.41–3.45 (m, 2 H, CH_2), 2.90 (t, J = 5.9 Hz, 2 H, CH_2), 2.87 (t, J = 6.2 Hz, 2 H, CH_2), NH not observed; HRMS (FAB$^+$) calcd for $C_{26}H_{25}N_7O_3$ (MH$^+$) m/z 497.2050, found 497.2058. Anal. calcd for $C_{26}H_{24}N_8O_3$: C, 62.9; H, 4.9; N, 22.7; found:C, 62.9, H, 4.9; N, 22.7.

Example AL

***N*-[2-({2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethyl}amino)ethyl]5-methyl-4-acridinecarboxamide (103).** 4-(1*H*-Imidazol-1-ylcarbonyl)-5-methylacridine (245 mg, 0.86 mmol) was added to a solution of amine **101** (113 mg, 0.43 mmol) in DMF (5 mL) and the reaction mixture stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0–2%) of aqueous NH_3/(0–4%) MeOH/DCM, to give compound **103** (156 mg, 75%) as a red solid, mp (DCM/hexane) 135–140 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.52 (t, J = 5.5 Hz, 1 H, CONH), 9.25 (s, 1 H, ArH), 8.74 (dd, J = 7.1, 1.6 Hz, 1 H, ArH), 8.36 (dd, J = 8.6, 1.5 Hz, 1 H, ArH), 8.18 (br, 1 H, NH), 8.10 (dd, J = 8.6, 0.9 Hz, 1 H, ArH), 8.03 (d, J = 8.4 Hz, 1 H, ArH), 7.96 (dd, J = 8.7, 1.2 Hz, 1 H, ArH), 7.90 (ddd, J = 7.8, 5.9, 1.4 Hz, 1 H, ArH), 7.73–7.77 (m, 2 H, ArH), 7.49–7.57 (m, 2 H, ArH), 3.65 (br q, J = 6.0 Hz, 2 H, CH_2), 3.47–3.51 (m, 2 H, CH_2), 2.92 (t, J = 6.0 Hz, 2 H, CH_2), 2.88 (s, 3 H, CH_3), 2.86 (t, J = 6.3 Hz, 2 H, CH_2), NH not observed;

^{13}C NMR [$(CD_3)_2SO$] δ 164.8, 149.8, 146.4, 144.6, 138.7, 137.8, 135.4, 135.2, 134.5, 132.6, 131.1, 129.7, 128.2, 126.7, 126.4, 126.2 (2), 125.5, 125.1, 120.9, 116.6, 48.4, 47.8, 40.4, 39.6, 18.2; HRMS (FAB$^+$) calcd for $C_{26}H_{26}N_7O_3$ (MH$^+$) m/z 484.2097, found 484.2094.

Example AM

***N*-{5-[4-(Dimethylamino)butanoyl]-1-methyl-1*H*-pyrrol-3-yl}-4-({4-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]butanoyl}amino)-1-methyl-1*H*-pyrrole-2-carboxamide (112).**

Methyl 4-[({4-[(*tert*-Butoxycarbonyl)amino]-1-methyl-1*H*-pyrrol-2-yl}carbonyl)amino]-1-methyl-1*H*-pyrrole-2-carboxylate (106). A solution of methyl 4-amino-1-methyl-1*H*-pyrrole-2-carboxylate (**104**) (Baird & Dervan, *J. Am. Chem. Soc.* 1996, 118, 6141–6146) (792 mg, 4.2 mmol) and 4-[(*tert*-butoxycarbonyl)amino]-1-methyl-1*H*-pyrrole-2-carboxylic acid (**105**) (Baird & Dervan, *J. Am. Chem. Soc.* **1996**, 118, 6141–6146) (1.0 g, 4.2 mmol) in DMF (13 mL) and DCM (3 mL) was treated with EDCI (1.5 g, 6.2 mmol) and DMAP (0.77 g, 5.0 mmol). The reaction mixture was stirred at 20 °C for 18 h, poured into 10% HCl (20 mL) and extracted with EtOAc (3 × 40 mL). The combined organic fraction was washed with saturated aqueous $NaHCO_3$, dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–50%) of EtOAc/pet. ether to give amide **106** (1.0 g, 64%) as a white solid, mp (DCM/pet. ether) 89–90 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.82 (s, 1 H, NH), 9.06 (br s, 1 H, NH), 7.44 (d, J = 1.9 Hz, 1 H, ArH), 6.90 (d, J = 2.0 Hz, 1 H, ArH), 6.88 (br s, 1 H, ArH), 6.83 (br s, 1 H, ArH), 3.83 (s, 3 H, CH_3), 3.80 (s, 3 H, CH_3), 3.74 (s, 3 H, CO_2CH_3), 1.46 (s, 9 H, 3 × CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 168.7, 158.3, 152.7, 122.9, 122.5, 122.3, 120.6, 118.4, 117.1, 108.3, 103.8, 78.2, 50.8, 36.0, 35.9, 28.1 (3); HRMS (EI$^+$) calcd for $C_{18}H_{24}N_4O_5$ (M$^+$) m/z 376.1747, found 376.1744.

4-{[(4-Amino-1-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-1-methyl-1*H*-pyrrole-2-carboxylic Acid (107). A solution of LiOH (343 mg, 14.3 mmol) in water (7 mL) was added to a solution of amide **106** (1.0 g, 2.7 mmol) in THF/MeOH (3:1, 28 mL) and the mixture heated at 60 °C for 18 h. The mixture was cooled and diluted with EtOAc (150 mL). The aqueous layer was separated, adjusted to the pH 3 with 10% aqueous

HCl and extracted with EtOAc (3 × 40 mL). The combined organic fraction was dried and the solvent evaporated to give acid **107** (900 mg, 94%) as a white solid, mp (DCM/hexane) 138–142 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.70 (br s, 1 H, CO_2H), 9.78 (s, 1 H, NH), 9.05 (s, 1 H, NH), 7.38 (d, J = 1.9 Hz, 1 H, ArH), 6.90 (br s, 1 H, ArH), 6.82 (d, J = 2.0 Hz, 2 H, ArH), 3.81 (s, 3 H, CH_3), 3.80 (s, 3 H, CH_3), 1.46 (s, 9 H, 3 × CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 171.8, 161.8, 158.3, 152.8, 122.6, 122.3, 120.1, 119.4, 117.0, 108.3, 103.7, 78.2, 36.0, 35.9, 28.1 (3); HRMS (FAB$^+$) calcd for $C_{17}H_{23}N_4O_5$ (MH$^+$) *m/z* 363.1669, found 363.1653.

***tert*-Butyl 5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-ylcarbamate (108).** A solution of acid **107** (900 mg, 2.5 mmol) was treated with EDCI (950 mg, 5.0 mmol), DMAP (758 mg, 6.2 mmol) and 3-dimethylaminopropylamine (507 mg, 5.0 mmol). The reaction mixture was stirred at 20 °C for 18 h, diluted with EtOAc (100 ml) and washed with 10% aqueous HCl (3 × 20 mL). The combined aqueous fraction was basified with aqueous NH_3, extracted with EtOAc (3 × 40 mL), dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(0–5%) MeOH/DCM, to give amide **108** (847 mg, 76%) as a viscous oil, which solidified on standing, mp (DCM/pet.ether) 120-123 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.77 (s, 1 H, NH), 9.04 (br s, 1 H, NH), 8.01 (t, J = 5.6 Hz, 1 H, NH), 7.15 (d, J = 1.8 Hz, 1 H, ArH), 6.87 (br s, 1 H, ArH), 6.81 (d, J = 1.8 Hz, 2 H, ArH), 3.80 (s, 3 H, CH_3), 3.79 (s, 3 H, CH_3), 3.18 (br q, J = 6.5 Hz, 2 H, CH_2), 2.24 (t, J = 7.1 Hz, 2 H, CH_2), 2.13 [s, 6 H, $N(CH_3)_2$] 1.89 (br quin, J = 7.0 Hz, 2 H, CH_2), 1.46 (s, 9 H, 3 × CH_3).

Methyl 4-[(1-Oxido-1,2,4-benzotriazin-3-yl)amino]butanoate (109). A solution of chloride **3** (1.57 g, 8.7 mmol), methyl 4-aminobutanoate hydrochloride (1.73 g, 11.4 mmol) and Et_3N (3.14 mmol, 22.5 mmol) in DME (50 mL) was heated at 90 °C for 6 h. The solvent was evaporated and the residue was partitioned between DCM (100 mL) and water (50 mL). The organic fraction was separated and the aqueous layer was further extracted with DCM (4 × 30 mL). The combined organic fraction was dried, the solvent evaporated and the residue purified by chromatography, eluting with a gradient (0–2%) of MeOH/DCM, to give ester **109** (1.9 g, 81%) as a yellow solid,

mp (DCM/pet. ether) 122–126 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.11 (dd, J = 8.6, 1.1 Hz, 1 H, H-8), 7.90 (br s, 1 H, NH), 7.76 (ddd, J = 7.7, 7.1, 1.5 Hz, 1 H, H-6), 7.54 (br d, J = 8.3 Hz, 1 H, H-5), 7.31 (ddd, J = 7.9, 7.0, 1.2 Hz, 1 H, H-7), 3.58 (s, 3 H, OCH_3), 3.34–3.38 (m, 2 H, CH_2), 2.41 (t, J = 7.4 Hz, 2 H CH_2), 1.86–1.91 (m, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 173.2, 159.1, 148.4, 138.2, 135.7, 126.1, 124.6, 120.0, 51.3, 40.0, 30.8, 24.0; HRMS (EI^+) calcd for $C_{12}H_{14}N_4O_3$ (M^+) m/z 262.1066, found 262.1066. Anal. calcd for $C_{12}H_{14}N_4O_3$: C, 55.0; H, 5.4; N, 21.4; found:C, 55.1; H, 5.4; N, 21.4%.

Methyl 4-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]butanoate (110). Hydrogen peroxide (70%, 3.1 mL, 65 mmol) was added dropwise to a stirred solution of trifluoroacetic anhydride (9.0 mL, 65 mmol) in DCM (15 mL) at 0 °C and the solution stirred at 0 °C for 10 minutes. The solution was added to a solution of ester **109** (1.7 g, 6.5 mmol) in DCM (30 mL) at 20 °C and stirred for 16 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (100 mL), the organic layer separated and the aqueous layer further extracted with DCM (3 × 30 mL). The combined organic fraction was dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–2%) of MeOH/DCM, to give (i) starting material **109** (610 mg, 36%); and (ii) 1,4-dioxide **110** (592 mg, 33%) as a red solid, mp (DCM/pet. ether) 169–171 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.33 (t, J = 4.1 Hz, 1 H, NH), 8.20 (dd, J = 8.8, 0.7 Hz, 1 H, H-8), 8.12 (dd, J = 8.7, 0.7 Hz, 1 H, H-5), 7.93 (ddd, J = 7.8, 7.1, 1.4 Hz, H-6), 7.56 (ddd, J = 7.8, 7.1, 1.3 Hz, 1 H, H-7), 3.59 (s, 3 H, OCH_3), 3.42 (br q, J = 6.6 Hz, 2 H, CH_2), 2.40 (t, J = 7.4 Hz, 2 H, CH_2), 1.88 (br quin, J = 7.1 Hz, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 173.0, 149.8, 138.2, 135.4, 129.9, 126.9, 121.1, 116.8, 51.2, 39.9, 30.5, 23.9; HRMS (EI^+) calcd for $C_{12}H_{14}N_4O_4$ (M^+) m/z 278.1015, found 278.1014. Anal. calcd for $C_{12}H_{14}N_4O_4$: C, 51.8; H, 5.1; N, 20.1; found:C, 51.6; H, 4.9; N, 20.1%.

4-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]butanoic Acid (111). A mixture of 1,4-dioxide **110** (351 mg, 1.26 mmol) and 1 N NaOH (6.3 mL, 6.30 mmol) in MeOH (20 mL) was stirred at 20 °C for 18 h. 10% Aqueous HCl (7 mL) was added and MeOH was evaporated. The resulting red precipitate was filtered, washed with water and dried to give acid **111** (270 mg, 81%) yield, mp (H_2O) 185–188 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.82 (br s, 1 H, NH), 8.19 (dd, J = 8.8, 0.6 Hz, 1 H, H-8), 8.11 (dd, J =

8.4, 0.9 Hz, 1 H, H-5), 7.92 (ddd, J = 7.8, 7.1, 1.4 Hz, 1 H, H-6), 7.54 (ddd, J = 7.8, 7.2, 1.3 Hz, 1 H, H-7), 3.38 (t, J = 6.9 Hz, 2 H, CH_2), 1.99 (t, J = 7.0 Hz, 1 H, CH_2), 1.79 (br quin, J = 7.0 Hz, 2 H, CH_2); HRMS (EI) calcd for $C_{11}H_{12}N_4O_4$ (M^+) m/z 264.0845, found 264.0850. Anal. calcd for $C_{11}H_{12}N_4O_4$: C, 50.0, H, 4.6, N, 21.2; found:C, 50.1; H, 4.5, N, 21.2%.

***N*-{5-[4-(Dimethylamino)butanoyl]-1-methyl-1*H*-pyrrol-3-yl}-4-({4-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]butanoyl}amino)-1-methyl-1*H*-pyrrole-2-carboxamide (112).** Carbamate **108** (166 mg, 0.37 mmol) was dissolved in HCl/MeOH (3 mL) and stirred for 16 h. The solvent was evaporated and the residue was dissolved in MeOH (5 mL) and evaporated. This process was repeated two more times. The residue was dissolved in DMF (5 mL) and DCM (2 mL) and acid **111** (264 mg, 0.38 mmol), EDCI (146 mg, 0.76 mmol) and DMAP (93 mg, 0.76 mmol) were added and the mixture stirred for 16 h at 20 °C. The solvent was evaporated and the residue was partitioned between DCM and aqueous NH_3. The resulting precipitate was collected by filtration and purified by chromatography, eluting with a gradient (0–1%) of aqueous NH_3/(0–5%) MeOH/DCM, to give compound **112** (21 mg, 9%) as an orange solid, mp (DCM/pet. ether) 140–145 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.81 (s, 1 H, ArH), 9.79 (s, 1 H, ArH), 8.35 (t, J = 6.1 Hz, 1 H, NH), 8.21 (d, J = 8.5 Hz, 1 H, H-8), 8.14 (d, J = 8.1 Hz, 1 H, H-5), 8.03 (t, J = 5.7 Hz, 1 H, NH), 7.94 (ddd, J = 7.8, 7.1, 0.8 Hz, 1 H, H-6), 7.59 (ddd, J = 7.9, 7.1, 1.3 Hz, 1 H, H-7), 7.25 (d, J = 1.8 Hz, 1 H, ArH), 7.13 (d, J = 1.8 Hz, 1 H, ArH), 6.85 (d, J = 1.8 Hz, 1 H, ArH), 6.81 (d, J = 1.8 Hz, 1 H, ArH), 3.81 (s, 3 H, CH_3), 3.79 (s, 3 H, CH_3), 3.46 (br q, J = 6.6 Hz, 2 H, CH_2), 3.19 (br q, J = 6.5 Hz, 2 H, CH_2), 2.32 (br q, J = 6.9 Hz, 4 H, 2 × CH_2), 2.19 [s, 6 H, $N(CH_3)_2$], 1.93 (br quin, J = 7.2 Hz, 2 H, CH_2), 1.63 (br quin, J = 7.0 Hz, 2 H, CH_2), 3-NH not observed; ^{13}C NMR [$(CD_3)_2SO$] δ 169.0, 161.1, 158.3, 149.7, 138.1, 135.3, 129.8, 126.8, 122.9, 122.6, 121.9, 121.8, 121.0, 118.0, 117.6, 116.8, 103.9 (2), 56.8, 44.9 (2), 40.5, 36.9, 35.9, 35.8, 32.9, 26.9, 25.0; HRMS (FAB$^+$) calcd for $C_{28}H_{37}N_{10}O_5$ (MH^+) m/z 593.2948, found 593.2953. Anal. calcd for $C_{28}H_{36}N_{10}O_5 \cdot H_2O$: C, 55.1; H, 6.3; N, 22.9; found:C, 55.1; H, 6.6, N, 22.2.%.

Example AN

***tert*-Butyl 2-[(3-Ethyl-1,4-dioxido-1,2,4-benzotriazin-7-yl)oxy]ethylcarbamate (117).**

***N*-{2-[(3-Amino-1-oxido-1,2,4-benzotriazin-7-yl)oxy]ethyl}-2,2,2-trifluoroacetamide (113).** A mixture of compound **46** (520 mg, 3.0 mmol), K_2CO_3 (833 mg, 6.0 mmol) and *N*-(2-bromoethyl)-2,2,2-trifluoroacetamide (1.25 g, 4.0 mmol) in DMF (20 mL) was stirred at 100 °C for 16 h. The solvent was evaporated and the residue suspended in water. The suspension was extracted with EtOAc (3 × 50 mL), the organic fraction dried and the solvent evaporated. The residue was purified by chromatography, eluting with 5% MeOH/DCM, to give compound **113** (639 mg, 66%) as a tan solid, mp (DCM/pet. ether) 234–236 °C. Anal. calcd for $C_{11}H_{10}F_3N_5O_3$: C, 41.7; H, 3.2; N, 22.1; F, 18.0; found: C, 41.9; H, 3.0; N, 21.9; F, 17.5%.

***N*-{2-[(3-Chloro-1-oxido-1,2,4-benzotriazin-7-yl)oxy]ethyl}-2,2,2-trifluoroacetamide (114).** A solution of $NaNO_2$ (652 mg, 9.5 mmol) in water (20 mL) was added dropwise to a stirred suspension of amine **113** (1.5 g, 4.7 mmol) in 2 M HCl (75 mL) at 0 °C and the mixture stirred at 20 ° for 16 h. The suspension was filtered, the solid washed with water (2 × 10 mL) and dried to give 2,2,2-trifluoro-*N*-{2-[(3-hydroxy-1-oxido-1,2,4-benzotriazin-7-yl)oxy]ethyl}acetamide (1.44 g, 100%) as a tan solid, mp 202–204 °C. Anal. calcd for $C_{11}H_9F_3N_4O_4$: C, 41.5; H, 2.9; N, 17.6; F, 17.9; found: C, 41.8; H, 2.9; N, 17.4; F, 17.6%.

A mixture of the 3-hydroxide (1.39 g, 4.1 mmol) and $POCl_3$ (15 mL) was stirred at 100 °C for 2 h. The solution was cooled and poured into ice/water and stirred for 30 min. The precipitate was filtered, washed with water, and dried. The solid was purified by chromatography, eluting with a gradient (0–10%) of EtOAc/DCM, to give chloride **114** (1.37 g, 100%) as a tan solid, mp 179–181 °C. Anal. calcd for $C_{11}H_8ClF_3N_4O_3$: C, 39.2; H, 2.4; N, 16.6; F, 16.9; found: C, 39.5; H, 2.5; N, 16.7; F, 16.9%.

***N*-{2-[(3-Ethyl-1-oxido-1,2,4-benzotriazin-7-yl)oxy]ethyl}-2,2,2-trifluoroacetamide (115).** $Pd(PPh_3)_4$ (198 mg, 0.17 mmol) was added to a purged solution of chloride **114** (1.16 g, 3.4 mmol) and Et_4Sn (0.82 mL, 4.1 mmol) in DME (50 mL) and the mixture heated at reflux temperature under N_2 for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with 1%

MeOH/DCM, to give compound **115** (896 mg, 79%) as a cream solid, mp (DCM) 155–157 °C. Anal. calcd for $C_{13}H_{13}F_3N_4O_3$: C, 47.3; H, 4.0; N, 17.0; found: C, 47.4; H, 4.2; N, 17.1%.

***tert*-Butyl 2-[(3-Ethyl-1-oxido-1,2,4-benzotriazin-7-yl)oxy]ethylcarbamate (116).** A solution of compound **115** (370 mg, 1.1 mmol) in 0.5 M K_2CO_3 solution (15 mL) was stirred at 20 °C for 16 h. The solution was extracted with $CHCl_3$ (3 × 30 mL), the organic fraction dried and the solvent evaporated. The residue was dissolved in THF (50 mL) and di-*tert*-butyl dicarbonate (367 mg, 1.68 mmol) added and the solution stirred at 20 °C for 5 h. The solution was partitioned between EtOAc and water, the organic fraction dried and the solvent evaporated. The residue was purified by chromatography, eluting with 10% EtOAc/DCM, to give carbamate **116** (330 mg, 88%) as a white solid, mp. 101–103 °C.

***tert*-Butyl 2-[(3-Ethyl-1,4-dioxido-1,2,4-benzotriazin-7-yl)oxy]ethylcarbamate (117).** A mixture of 1-oxide **116** (300 mg, 0.9 mmol) and MCPBA (663 mg, 2.7 mmol) in DCM (20 mL) was stirred at 20 °C for 36 h. The solution was partitioned between dilute aqueous NH_3 and DCM, the organic fraction dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–20%) of EtOAc/DCM, to give 1,4-dioxide (239 mg, 76%) as a red powder, mp (DCM/pet. ether) 111-113 °C.

Example AO: Cytotoxicity of Compounds

Evaluation of the cytotoxicity of compounds by clonogenic assay under aerobic and hypoxic conditions.

Compounds representative of the invention were evaluated under both aerobic and hypoxic conditions in clonogenic assays, using three cell lines: human colon carcinoma HT-29, murine SCCVII, and human lung adenocarcinoma LXFL. Clonogenic survival was determined using aerobic and hypoxic SCCVII cell suspensions. Drug exposures were performed using continuously stirred and gassed single cell suspensions (10^6 cells/mL) at 37 °C, equilibrated with 5% CO_2 in air or N_2 for 60 min before drug addition. After a 60 min drug exposure cells were washed by centrifugation and plated to determine colony formation. Cytotoxicity was measured

as the concentration required to reduce plating efficiency to 10% of controls (C_{10}). The hypoxic cytotoxicity ratio (HCR) was determined as the ratio of the C_{10} values under aerobic and hypoxic conditions. The relative hypoxic toxicity (RHT) was determined as the ratio of hypoxic TPZ C_{10} to hypoxic BTO C_{10}. The results of these assays are given in Table 2. Abbreviations used in Table 2 are:

C_{10} = The concentration of drug (in micromolar) to reduce viable cell numbers to 10% of those of control cell cultures grown under the same conditions but not exposed to drug

RHT = Relative hypoxic toxicity is defined as the ratio of concentrations of Tirapazamine/test compound to give equal cell killing under hypoxic conditions.

HCR = Hypoxic cytotoxicity ratio is defined as the ratio of drug concentrations under aerobic and hypoxic condition to produce equal cell survival (10%) determined by clonogenic assay

Table 2. Cytotoxicities of compounds of the invention under hypoxic conditions, hypoxic toxicity relative to Tirapazamine (RHT) and hypoxic selectivity (HCR) in clonogenic assay

HT 29 cells			
compound	**C_{10} hypoxic (μM)**	**RHT**	**HCR**
11	0.12	416	83.0
30	0.9	78	33.0
SCVIII cells			
compound	**C_{10} hypoxic (μM)**	**RHT**	**HCR**
	SN (hypoxic)		
11	0.48	16.7	20.0
17	4.8	1.94	>6.3
30	0.3	20	21.3
41	0.8	12.5	52.5

44	0.16	56.3	>187
43	1.4	5.7	10
45	0.31	29	23.9
55	1.1	10	63.6
95	1.0	11	400
96	2.3	3.9	65
99	0.29	17.2	176
LXFL cells			
compound	**C_{10} hypoxic (μM)**	**RHT**	**HCR**
11	0.04	450	35.0
30	0.4	50	12.5
41	0.4	37.5	50

The results of Table 2 clearly show that the compounds of the invention show large increases in cytotoxicity compared with Tirapazamine, while retaining selective killing under hypoxic conditions.

Example AP: Cytotoxicity of Compounds

Evaluation of the cytotoxicity of compounds by proliferation assay (IC_{50}) under aerobic and hypoxic conditions.

Compounds representative of the invention were evaluated under both aerobic and hypoxic conditions in a proliferation assay (IC_{50}), using two cell lines: human colon carcinoma HT-29, and human cervical carcinoma SiHa.

Drug exposures were performed in 96-well plates (Nunc) using either a 37 °C humidified incubator (20% O_2, 5% CO_2) or in the incubator compartment (37 °C) of an anaerobic chamber (Shell Lab) where palladium catalyst scrubbed gas (90% N_2, 5% H_2, 5% CO_2) ensures severe anoxia (<0.001% O_2). For each experiment, compounds were simultaneously tested under both oxic and hypoxic conditions against the HT-29 cell line and included TPZ as an independent internal control at the

front and back of the assay (n = 2). Final data was pooled from a series of seven independent experiments and is calculated using inter-experimental means. In all cases, 8-methyl-5-nitroquinoline was used as a second internal control to confirm that strict hypoxia was present during the experiment. (Siim et al., *Br. J. Cancer* **1994**, *70*, 596–603). Cell cultures were grown in αMEM (Gibco) containing 5% heat inactivated FCS and maintained in exponential growth phase. For each individual experiment an appropriate number of cells were seeded (HT-29 = 1000) into wells in αMEM + 10% FCS + 10 mM added glucose + 100 μM 2′-deoxycytidine (2′dCyd), and allowed to attach for 3 h. High glucose (final concentration 17 mM) and the presence of 2′-dCyd minimize hypoxia-induced cell cycle arrest. Replicates were then exposed to BTOs, using 2-fold serial dilutions in triplicate, for a further 4 h. Subsequently cells were washed free of compound using complete media (without glucose/2′-dCyd) and allowed to grow for 5 (oxic) or 6 (anoxic) days. Plates were stained as described previously (Wilson et al., *J. Med. Chem.* **1989**, *32*, 31–38) and IC_{50} values determined.

IC_{50} = The concentration of drug (in micromolar) to reduce viable cell numbers to 50% of those of control cell cultures grown under the same conditions but not exposed to drug

RHT = Relative hypoxic toxicity is defined as the ratio of concentrations of Tirapazamine/test compound to give equal cell killing under hypoxic conditions.

HCR = Hypoxic cytotoxicity ratio is defined as the ratio of drug concentrations under aerobic and hypoxic condition to produce equal cell survival (50%) determined by proliferation assay

Table 3. Cytotoxicities of compounds of the invention under hypoxic conditions, hypoxic toxicity relative to Tirapazamine (RHT) and hypoxic selectivity (HCR) in proliferation assay

HT-29 IC_{50}			
Compound	**IC_{50} hypoxic (μM)**	**RHT**	**HCR**
11	0.016	370	38
30	0.065	90	167
31	0.356	163	5.3
37	0.079	74	160
41	0.043	134	154
42	0.517	11.2	86.2
43	0.113	51.4	119
44	0.226	25.7	72.7
45	0.018	321	31
55	0.124	47	97
62	0.021	274	157
63	0.034	167	129
74	0.130	44.7	95
75	0.200	29	92
85	0.222	26	134
86	0.225	66	168
95	0.18	71	74
96	0.19	31	77
98	0.135	114	45
99	0.41	14	25
102	0.49	12	54
103	0.035	357	83
SiHa IC_{50}			
Compound	**IC_{50} hypoxic (μM)**	**RHT**	**HCR**
30	0.031	121	41

55	0.05	72	124
75	0.07	53	110
86	0.105	35	136
95	0.076	48	89
96	0.10	37	78
98	0.075	63	30
102	0.16	23	53
103	0.01	309	118

The results of Table 3 clearly show that the compounds of the invention show large increases in cytotoxicity compared with Tirapazamine, while retaining selective killing under hypoxic conditions.

Wherein the foregoing description reference has been made to reagents, or integers having known equivalents thereof, then those equivalents are herein incorporated as if individually set forth.

While this invention has been described with reference to certain embodiments and examples, it is to be appreciated that further modifications and variations can be made to embodiments and examples without departing from the scope of the invention.